Activation Date: 02/15/2010
Includes Update #05

CANCER AND LEUKEMIA GROUP B

CALGB 100701/BMT CTN 0804

PHASE II STUDY OF REDUCED-INTENSITY ALLOGENEIC STEM CELL TRANSPLANT FOR HIGH-RISK CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Rituximab provided by Genentech and distributed by Biologics Inc.

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

Study Chair
Edwin P. Alyea, MD
Medical Oncology
Dana Farber Cancer Institute
44 Binney Street
Boston, MA
Tel: 617-632-3903 Fax: 617-632-5175
edwin_alyea@dfci.harvard.edu

BMT CTN Co-Chair
Richard T. Maziarz, MD
Oregon Health & Science University
3181 SW Sam Jackson Park Rd
Mail Code UHN73C
Portland, Oregon 97239
Tel: 503-494-4606 Fax: 504-494-1552
maziarzr@ohsu.edu

Correlative Science Study Co-Chair
John Gribben, MD
Cancer Research UK Med Oncology Unit,
Barts and The London School of Medicine,
Charterhouse Square,
London EC1M 6BQ
Fax: +44(0)207-882-6126
john.gribben@cancer.org.uk

Transplant Committee Chair
Steven M. Devine, MD
Tel: 614-293-5655 Fax: 614-293-6690
steven.devine@osumc.edu

Leukemia Committee Chair
Richard Larson, MD
Tel: 773-702-6783 Fax: 773-702-3002
rlarson@medicine.bsd.uchicago.edu

Leukemia Correlative Sciences Committee Chair
Guido Marcucci, MD
Tel: 614-366-2261 Fax: 614-688-4028
guido.marcuccii@osumc.edu

Faculty Statistician
Kouros Owzar, PhD
Tel: 919-681-1829 Fax: 919-681-8028
kouros.owzar@duke.edu

Staff Statistician
Hyuna Yang, PhD
Tel: 919-681-6626 Fax: 919-681-7918
hy57@notes.duke.edu

Data Coordinator
Elizabeth Bennett, BHE, CCRP
Tel: 919-668-9379 Fax: 919-668-9348
elizabeth.bennett2@duke.edu

Protocol Coordinator
Morgen Alexander-Young, MPH
Tel: 773-702-4236 Fax: 312-345-0117
malexanderyoung@uchicago.edu

For NCI Use Only
Version Date: 01/04/12

CALGB Central Office
230 W. Monroe Street, Suite 2050
Chicago, IL 60606-4703
(773) 702-9171
Fax: (312) 345-0117
www.calgb.org

AE Reporting:
http://ctep.info.nih.gov/reporting/adeers.html
CAEPR for rituximab may be found in Section 16.3

CALGB Statistical Center
Hock Plaza
2424 Erwin Road, Suite 802
Durham, NC 27705
Tel: 919-681-9350
Data Operations Fax: 919-668-9348
Biostatistics Fax: 919-681-8028

Patient Registration: (919) 668-9396
Patient Registration Fax: (919) 668-9397

CALGB Leukemia Tissue Bank
Michael A. Caligiuri, MD
The Arthur G. James Cancer Hospital and Research Institute
300 West Tenth Avenue, Lobby
Phone: 614-688-4754
Fax: 614-688-4755
calgb.ltb@osumc.edu

BMT CTN Data Coordinating Center
The EMMES Corporation
401 N. Washington St., Suite 700
Rockville, MD 20850
Tel: 301-251-1161
Fax: 301-251-1355

CALGB Nurse Liaison
Vicki Lagerwey, RN, BSN, OCN
Phone: 336-716-5947
Fax: 336-716-6278
vlagerwe@wfubmc.edu

The correlative science component of this study is conducted by the Chronic Lymphocytic Leukemia Research Consortium (CLLRC)

PHASE II STUDY OF REDUCED-INTENSITY ALLOGENEIC STEM CELL TRANSPLANT FOR HIGH-RISK CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Schema Page 1 of 3

Patient Eligibility

Diagnosis of B-CLL or B-SLL according to IWCLL 2008 Criteria:

Early Disease Cohort *(must include one or more of the following)*:

- FISH showing deletion of 17p in ≥ 20% of cells (either at diagnosis or any time prior to study entry) either alone or in combination with other cytogenetic abnormalities.
- FISH showing del11q in ≥ 20% of cells (either at diagnosis or any time prior to study entry) either alone or in combination with other cytogenetic abnormalities unless the patient has achieved a complete remission by IWCLL 2008 Criteria which includes CT scan, bone marrow morphology and flow cytometry.
- Failure to achieve a partial response with initial chemotherapy, but with lack of progression. These patients may receive a second therapy to improve their response prior to transplant.
- In addition, patients in the early disease cohort *must have all of the following:*
  - receive at least 2 cycles of induction therapy (see Section 4.1.1.4);
  - stable disease or better by NCI Criteria to most recent therapy (i.e., no prior progression);
  - nodes ≤ 5 cm.

Advanced Disease Cohort *(must include one or more of the following)*:

- FISH showing deletion of 17p in ≥ 20% of cells (regardless of interval from initial therapy) either alone or in combination with other cytogenetic abnormalities.
- First progression < 24 months after initial regimen. This includes progression on initial therapy.
- Second or subsequent progression.
- In addition, patients in the advanced disease cohort *must have all of the following:*
  - stable disease or better by NCI Criteria to their most chemotherapy;
  - nodes ≤ 5 cm.

ECOG Performance Status 0-2.
Age ≥ 18 years and < 70.
At least 4 weeks after start of last cycle of cytotoxic chemotherapy, or alemtuzumab.
No HIV infection (see Section 4.5).
No hepatitis B sAg, anti-HBc or HCV Ab positive.
DLCO ≥ 40% predicted.
LVEF by ECHO or MUGA ≥ 30%
No uncontrolled diabetes mellitus or active uncontrolled serious infections.
Non-pregnant and non-nursing.

Initial Required Laboratory Values

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

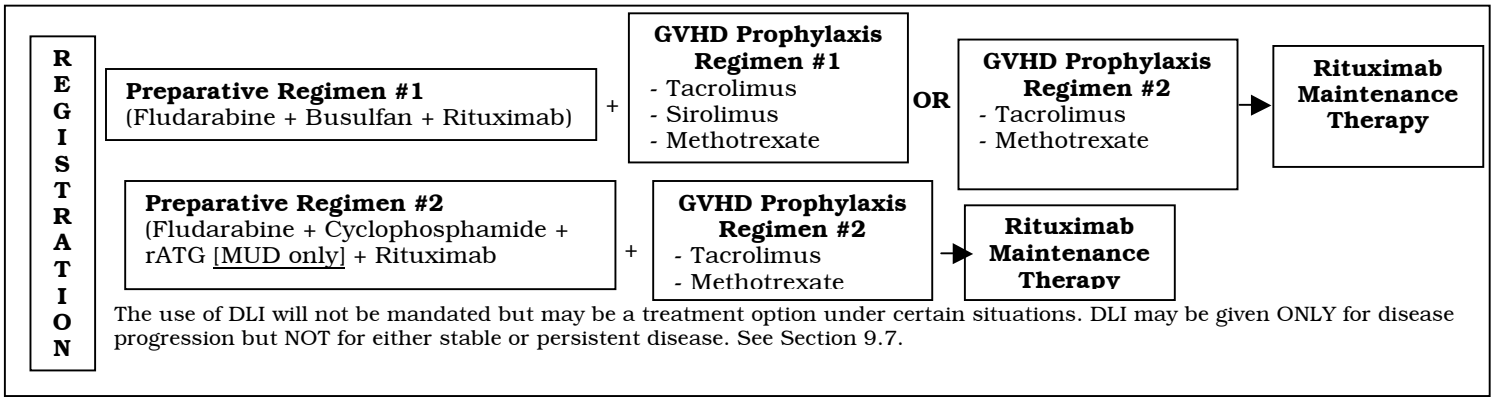
**except for Gilbert's syndrome*

Donor Eligibility Criteria (Sec. 5.0)

Donors may be either a 6/6 HLA-matched related donor.
Donors may be a 8/8 matched unrelated donor at HLA A, B, C, DR.
Unrelated donors will be analyzed by molecular typing at both HLA Class I and Class II (A, B, C, DR loci).
Donors must be healthy and must be an acceptable donor as per institution standards for stem cell donation.
Syngeneic donors are not eligible.
There is no donor age restriction.

SCHEMA

Patients must be registered prior to initiation of preparative regimen. In any patient, institutions may elect to use EITHER Preparative Regimen #1 OR Preparative Regimen #2.



The use of DLI will not be mandated but may be a treatment option under certain situations. DLI may be given ONLY for disease progression but NOT for either stable or persistent disease. See Section 9.7.

PHASE II STUDY OF REDUCED-INTENSITY ALLOGENEIC STEM CELL TRANSPLANT FOR HIGH-RISK CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Schema Page 2 of 3

MOBILIZATION

Only peripheral blood grafts will be allowed. Bone marrow grafts will not be allowed. Any mobilization regimen will be allowed. A minimum CD34+ cell dose of 2 x 10^6/kg recipient weight should be collected with a goal of collecting ≥ 5 x 10^6/kg. Cells may be collected either prior to transplant and cryopreserved or collected fresh according to institutional practice. It is suggested that the infused cell dose be < 8 x 10^6/kg, but there is no specified cap on the cell dose.

PREPARATIVE REGIMENS

Two different preparative regimens will be allowed. Institutions may elect to use either preparative regimen 1 or preparative regimen 2. Chemotherapy doses for both regimens will be based on actual weight unless patient weight is ≥ 150% of ideal body weight (see Appendix II) in which case a corrected weight will be calculated as ideal weight + 25% (actual weight - ideal weight).

Two regimens for GVH prophylaxis will be allowed. However, GVHD prophylaxis regimen 1 (tacrolimus, sirolimus, methotrexate) may be used **ONLY** in conjunction with preparative regimen 1 (fludarabine, busulfan, rituximab). Prophylaxis regimen 2 may be used with either preparative regimen 1 or preparative regimen 2.

Preparative Regimen 1 (see Section 9.2.1) + GVHD Prophylaxis Regimen 1 (see Section 9.3.1)

	R						**R**								**R**						**R**
			F →																		
			B →																		
						T — *starting on Day -2 to achieve a target level of 5-10 ng/mL* →																
						S — *starting on Day -2 to achieve a target level of 3-12 ng mL* →															
								PBSCT													
									M		**M**			**M**							
Day	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**

R Rituximab 500 mg/m^2/day IV on Days -7, -1, +7, and +14 at an infusion rate and with pre-treatment according to institutional preferences.

F Fludarabine 30 mg/m^2/day IV over 30 minutes on Days -5 through -2.

B Busulfan 0.8 mg/kg/day IV over 3 hours on Days -5 through -2.

T Tacrolimus starting on Day -2 either orally or IV to achieve a target serum level of 5-10 ng/mL. In the absence of graft versus host disease, tacrolimus should be tapered by 1/3 between Days +60 and +90, and should be tapered to zero between Days +150 and +180, as clinically permissible.

S Sirolimus loading dose of 12 mg PO on Day -2 followed by an oral dose of 4 mg/day. See Section 9.3.1 for dosing based on clinical toxicity, GVHD concurrent medications, medical conditions, prior drug levels, drug-drug interactions and blood levels with a target of 3-12 ng/mL. In the absence of graft versus host disease, sirolimus should be tapered by 1/3 between Days +60 and +90, and should be tapered to zero between Days +150 and +180, as clinically permissible.

PBSCT Peripheral Blood Stem Cell Transplant. On Day 0 a minimum **total** CD34+ cell dose of ≥ 2 x 10^6/kg (actual weight - recipient) will be infused.

M Methotrexate 5 mg/m^2/day IV on Days +1, +3, and +6. Methotrexate doses may be adjusted or leucovorin added according to institutional guidelines. Hydrate intravenously and induce diuresis.

PHASE II STUDY OF REDUCED-INTENSITY ALLOGENEIC STEM CELL TRANSPLANT FOR HIGH-RISK CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Schema Page 3 of 3

Preparative Regimen 1 (see Section 9.2.1) + GVHD Prophylaxis Regimen 2 (see Section 9.3.2)

	R						R								R							R
			F →																			
			B →																			
						T ——— *starting on Day -2 to achieve a target level of 5-10 ng/mL* →																	
								PBSCT														
									M		M			M					M			
Day	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**

R Rituximab 500 mg/m^2/day IV on Days -7, -1, +7, and +14 at an infusion rate and with pre-treatment according to institutional preferences.

F Fludarabine 30 mg/m^2/day IV over 30 minutes on Days -5 through -2.

B Busulfan 0.8 mg/kg/day IV over 3 hours on Days -5 through -2.

T Tacrolimus starting on Day -2 either orally or IV to achieve a target serum level of 5-10 ng/mL. In the absence of graft versus host disease, tacrolimus should be tapered by 1/3 between Days +60 and +90, and should be tapered to zero between Days +150 and +180, as clinically permissible.

PBSCT Peripheral Blood Stem Cell Transplant. On Day 0 a minimum **total** CD34+ cell dose of ≥ 2 x 10^6/kg (actual weight - recipient) will be infused.

M Methotrexate 5 mg/m^2/day IV on Days +1, +3, +6 and +11. Methotrexate doses may be adjusted or leucovorin added according to institutional guidelines. Hydrate intravenously and induce diuresis.

Preparative Regimen 2 (see Section 9.2.1) + GVHD Prophylaxis Regimen 2 (see Section 9.3.2)

	R						R								R							R
		rATG [MUD only]																				
			F →																			
			C →																			
						T ——— *starting on Day -2 to achieve a target level of 5-10 ng/mL* →																	
									PBSCT													
										M		M			M					M		
Day	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**

R Rituximab 500 mg/m^2/day IV on Days -7, -1, +7, and +14 at an infusion rate and with pre-treatment according to institutional preferences.

F Fludarabine 30 mg/m^2/day IV over 30 minutes on Days -5 through -2.

C Cyclophosphamide 1 g/m^2/day IV over 1-2 hours on Days -5, -4, and -3.

rATG **Unrelated Donors Only:** 1.5 mg/kg IV on Day -6, 2.0 mg/kg on Day -5, and 2.5 mg/kg on Day -4 . Total dose is 6 mg/kg. See Section 9.2.2.3 for premedication.

T Tacrolimus starting on Day -2 either orally or IV to achieve a target serum level of 5-10 ng/mL. In the absence of graft versus host disease, tacrolimus should be tapered by 1/3 between Days +60 and +90, and should be tapered to zero between Days +150 and +180, as clinically permissible.

PBSCT Peripheral Blood Stem Cell Transplant. On Day 0 a minimum **total** CD34+ cell dose of ≥ 2 x 10^6/kg (actual weight - recipient) will be infused.

M Methotrexate 5 mg/m^2/day IV on Days +1, +3, +6 and +11. Methotrexate doses may be adjusted or leucovorin added according to institutional guidelines. Hydrate intravenously and induce diuresis.

RITUXIMAB MAINTENANCE THERAPY (see Section 9.6)

Rituximab 500 mg/m^2 will be administered by IV infusion at months 3, 6, 9, and 12 post Day 0 of transplant. Rituximab will be given at an infusion rate and with pre-treatment according to institutional preferences. The rituximab infusion may be moved up or back by as many as two weeks to accommodate patient/clinic scheduling.

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Background and Rationale

Despite recent therapeutic advances that include monoclonal antibody therapy with alemtuzumab [1] and rituximab in combination with chemotherapy [2-4], chronic lymphocytic leukemia (CLL) remains an incurable disease with standard therapy. Although both autologous and allogeneic transplantation have been attempted as definitive therapy, the role and optimal timing of transplantation in the treatment of CLL remain unclear. Recently, attention has focused on allogeneic transplantation, given the demonstration of a robust graft versus leukemia (GVL) effect in CLL [5, 6]. In an effort to expand the role of allogeneic transplant to the age group affected by CLL, reduced-intensity conditioning (RIC) allogeneic transplantation has been explored [7-9].

Recent advances in the understanding of the biology of CLL have included the identification of prognostic factors that strongly predict outcomes, including overall survival. These prognostic factors include the gene mutation status of the IgV_H gene, expression of CD38 and ZAP-70, and genetic abnormalities as assessed by FISH [9-12]. Among these genetic abnormalities, deletions of 17p and 11q account for 25% of presenting cases of CLL and are associated with median times to progression of only 2 years [11, 13, 14], and these genetically defined subsets are currently the sub-group of CLL patients with the poorest prognosis. Furthermore, patients with these genetic abnormalities respond to fludarabine-based regimens less well than others and manifest short response durations [13]. Patients with these findings represent an excellent population in which to test the efficacy of up-front reduced-intensity allogeneic transplant, to determine whether this early intervention can favorably impact the natural history of the disease.

1.2 Reduced-Intensity Conditioning (RIC) Allogeneic Transplantation for the Treatment of CLL

Several reports have emerged detailing the results of patients with CLL treated with RIC allogeneic stem cell transplantation (SCT). In one study, 64 patients (44 related donors, 20 unrelated donors) with advanced CLL were treated with total body irradiation (TBI) with or without fludarabine [15]. These patients had a 2-year overall survival (OS) and event-free survival (EFS) of 60% and 52%, respectively. The 2-year relapse and non-relapse mortality were 18% and 22%, respectively.

The Dana-Farber Cancer Institute (DFCI) reported the results of 46 patients with advanced CLL who were treated with a conditioning regimen of fludarabine (30 mg/m^2 IV x 4 days) and busulfan (0.8 mg/kg/d IV x 4 days) [16]. Ninety-four percent received G-CSF mobilized peripheral blood stem cells while 6% received bone marrow. Graft vs host disease (GVHD) prophylaxis included tacrolimus plus low-dose methotrexate (65%) or cyclosporine plus prednisone (35%). The majority of patients (67%) had HLA-matched unrelated donors, while 33% had an HLA-matched related donor. The patients were heavily pretreated, with a median of 5 prior therapies; 98% of patients had received fludarabine, 96% alkylating agents, 80% rituximab, and 32% alemtuzumab. Twenty-two percent of patients had relapsed after a prior autologous stem cell transplant. Most patients had active disease at time of transplant, with only 17% in complete remission (CR) and 26% in partial remission (PR) at the time of transplantation. Fifty percent of patients were in active relapse and 7% had failed to respond to any attempted therapy (induction failures). At two years, the OS and progression-free survival (PFS) rates in this patient population were 54% and 34%, respectively, with a median follow-up of 20 months. In this heavily pretreated population, relapse was the principal cause of treatment failure, with a two-year cumulative incidence of 48%. Overall treatment-related mortality (TRM) was 17%.

Disease status at transplant proved to be a very strong predictor of both PFS and OS. Patients whose disease was at least in partial remission had a 3-year PFS of 60%. Other studies of RIC transplant in less heavily pretreated patients have also found that a greater number of prior therapies [17] and chemotherapy-refractory disease [18-20] are associated with worse outcome. Not surprisingly, the degree of bone marrow involvement was also a very significant predictor of both PFS and OS. The Seattle group has also identified bone marrow involvement and bulky lymphadenopathy as predictors of poor prognosis in CLL patients undergoing transplant [15]. To date, no one transplant conditioning regimen has been found to be superior to another.

The impact of adverse cytogenetics on transplant outcome is only starting to be explored. Two studies of less heavily pretreated patients have reported that adverse cytogenetics were not predictive of poor outcome, and in these studies selected patients with deletions of 11q or 17p remain in remission [15, 17]. In the DFCI study, in a multivariate analysis adverse cytogenetic features were not associated with reduced PFS [16]. Although this cytogenetic analysis and all other studies to date suffer from small patient numbers and incomplete data, nonetheless in each study selected patients with deletions of 11q or 17p have responded to allogeneic transplant [15, 17]. Although preliminary, these observations suggest that at least in some cases RIC allogeneic SCT may be able to overcome adverse cytogenetic features in CLL. Also given the better response rate for patients treated earlier in the course of their disease, upfront transplant in patients with adverse cytogenetics might result in improved outcomes. Similarly, several studies now suggest that allogeneic transplantation and the resulting graft-vs-leukemia (GVL) effect may be able to overcome the adverse prognostic effect of unmutated VH gene [17].

In this study, in order to encourage the widest participation, and because no one regimen has been shown to be superior, we will allow the use of either of two different RIC regimens. One regimen is the combination of busulfan plus fludarabine, which has been tested in the DFCI study of RIC allogeneic SCT for CLL [16]. This regimen allowed good engraftment from both related and unrelated donors, produced modest regimen-related toxicity, and was associated with good outcomes in patients with CLL whose disease was under reasonable control. We will also allow the use of a second RIC regimen of cyclophosphamide plus fludarabine. This regimen has been tested in CALGB 109901 in the setting of sibling donors and allows uniform engraftment. Outcomes in low-grade lymphoproliferative diseases, including CLL, were also encouraging. This regimen has also been extensively tested at MD Anderson Cancer Center in the treatment of follicular lymphomas and has produced very good results [19]. Because some cases of graft failure have been seen with this regimen when grafts were obtained from unrelated donors, we will add a low dose of rabbit anti-thymocyte globulin (rATG) in this setting. We will incorporate rituximab into both of these preparative regimens, based on the suggestion that the addition of rituximab to RIC regimens such as the cyclophosphamide/fludarabine regimen resulted in superior early disease control [21].

1.3 Methods to Prevent Graft-Versus-Host (GVH) Disease After Transplantation

Excessive treatment-related toxicity has limited the role of ablative allogeneic transplantation in patients with CLL. RIC regimens have greatly reduced treatment-related complications but significant issues such as the prevention of acute graft versus host disease (GVHD) remain. The majority of RIC transplant studies have used pharmacologic agents for GVH prophylaxis, such as cyclosporine plus methotrexate, cyclosporine plus corticosteroids or cyclosporine plus mycophenolate mofetil. Similar to conditioning regimens, no one GVH prophylaxis regimen has been identified to be superior to another regimen.

In this study, in order to encourage the widest participation, and because no one GVH prophylaxis regimen has been definitively shown to be superior, we will allow

the use of two different GVH prophylaxis regimens. The first will be the regimen tested at DFCI, the combination of tacrolimus plus sirolimus plus methotrexate. The regimen has been shown to be safe and tolerable when used with the low-dose busulfan plus fludarabine preparative regimen, and there is a suggestion that rates of GVH were lower than with other methods used. However, because excessive hepatotoxicity was seen in a trial in which a similar GVH prophylaxis strategy was used with an ablative busulfan plus cyclophosphamide preparative regimen, we will restrict the use of the sirolimus-containing GVH regimen to those who use the low-dose busulfan plus fludarabine preparative regimen with which it has been tested and shown to be safe. We will also allow of a second GVH prophylaxis regimen with tacrolimus plus methotrexate, and this standard regimen may be used with either preparative regimen.

1.4 Methods to Reduce Relapse After Transplant: Potential Role of Rituximab

Relapse of disease is the principle reason for treatment failure after transplant for CLL, and novel methods to reduce this risk are needed. Rituximab in combination with conventional chemotherapy has resulted in improved complete and overall response rates in patients with CLL compared with chemotherapy alone [2-4]. The mechanism by which rituximab improves response is not clear but increased ADCC has been suggested. Rituximab has been included in the preparative regimen for autologous transplantation for lymphoma in some trials. A recent report suggests that the inclusion of high-dose rituximab early after transplantation results in an improved outcome compared with historical controls [21]. Numerous studies are evaluating the role of rituximab as maintenance therapy both after conventional chemotherapy and transplantation as a method to reduce relapse. Rituximab given as adjuvant therapy to autologous stem cell transplant appears safe and in patients diagnosed with non-Hodgkin lymphoma (NHL) is associated with a 2-year EFS of 83% and OS of 83% [22]. Another study demonstrated that a single dose of rituximab administered ~8 weeks after autologous transplantation resulted in an increased number of patients with follicular or mantle cell lymphoma having no evidence of minimal residual disease (MRD) after transplantation [23]. In that trial, 22% of patients were MRD-negative prior to transplant, 53% following transplant, 72% following rituximab administration and 100% at 6 months after transplantation, suggesting that rituximab contributed to the elimination of MRD after transplantation.

The role of rituximab has also been explored in allogeneic transplantation. A previous report suggested that the addition of rituximab to a non-myeloablative regimen for patients with CLL resulted in a marked improvement in disease-free survival (DFS) [24]. Rituximab was administered on days –13 (375 mg/m^2), -6, +1 and +8 (1000 mg/m^2). OS was 100% for patients receiving chemotherapy and rituximab compared with 14% for those who received chemotherapy alone. The role of high dose rituximab compared to more conventional doses is unclear.

Rituximab has the potential of playing a dual role in the allogeneic situation not only by improving disease free survival by means of its anti-disease activity, but also preventing GVHD. Rituximab is an effective therapy for the treatment of chronic GVHD. A recent report demonstrated an overall response rate of 70% for patients with steroid refractory chronic GVHD receiving rituximab [25]. A trial exploring the role of maintenance rituximab for the prevention of chronic GVHD has been initiated.

1.5 Correlative Science in CALGB 100701 (CALGB 20802)

Previous experience with allogeneic transplant for CLL strongly suggests that the major source of efficacy is the allo-immune graft-versus-leukemia (GVL) effect rather than the effect of chemotherapy in the preparative regimen. Little is known, however, about the details of how this GVL effect is mediated. It is presumed that donor T cells reactive with CLL cells are the major effector mechanism, but it is not known to what

extent these T cells are directed against CLL-specific antigens versus HLA antigens. Also unknown is the possible contribution of donor B cell activity, possibly with an antibody-mediated mechanism.

In this substudy to CALGB 100701, we will attempt to characterize: 1) immune reconstitution following reduced intensity conditioning (RIC) transplants; 2) the target of the GVL effect in CLL, with specific emphasis on tumor specific responses; 3) whether a donor CLL specific immune response is associated with improved outcome after SCT; and 4) if response to transplant varies by genomic features such as interphase cytogenetics, IgV_H mutational status, apoptosis/immune SNPs and other features associated with drug resistance at the time of initiating transplant.

1.5.1 Background and Rationale

1.5.1.1 Allogeneic T Cell Responses Against CLL

Allo-SCT is associated with significant morbidity and mortality both from regimen-related toxicity as well as from GVHD and infection [26]. Encouraging results, however, have been observed even in refractory patients in whom there are no other treatment options available [27]. The encouraging results seen after RIC provides perhaps the strongest evidence of the power of the GVL effect in CLL [15, 28, 29].

1.5.1.2 Immune Responses Against CLL Associated Antigens

Autologous as well as allogeneic T cell responses can be generated against CLL cells using CD-40 activated CLL cells, dendritic cells (DCs) pulsed with CLL apoptotic bodies [30] or DCs pulsed with immunoglobulin or other tumor antigen derived peptides [31-33]. Antibody responses against CLL antigens Ags also can be demonstrated [32]. Following allogeneic SCT, the targets of the GVL are not known and could represent either minor histocompatibility antigens (mAG) expressed by the tumor cells, or tumor associated antigens (TAAg) expressed exclusively by the CLL cells. Using HLA-A2 tetramers we have demonstrated an increased frequency of donor T cells with specificity for idiotype (Id) peptides post SCT [31]. In 21 patients with CLL in whom we were able to produce Id tetramers, we were able to demonstrate Id specific CD8 T cell responses *in vivo* in 17 (80%) of these patients.

1.5.1.3 Antibody Responses Against Tumor Ags

Tumor associated Ags also can be detected by antibody responses using serological identification of Ags by recombinant expression cloning (SEREX) [34]. Serex has been successfully used to identify the targets of donor mediated immune responses following allogeneic donor lymphocyte infusions [35]. A modified Serex approach can be used to identify tumor associated Ags as well as examine the T cell responses against these Ags expressed in CLL [32].

1.5.1.4 High Risk Genomic Features and Response to Treatment

Recently, several groups have reported in small patient numbers that reduced intensity allogeneic stem cell transplant overcomes resistance associated with high risk genomic features that are linked to poor outcome [36, 37]. To confirm these findings prospectively and also to allow adequate patient characterization of subjects enrolled on this trial, a baseline bone marrow aspirate and peripheral blood sample will be obtained prior to initiating protocol therapy for examination of these features: interphase

cytogenetics, p53 mutations, ATM mutations, IgVH mutational status, ZAP70 expression, and complex karyotype as determined by CpG stimulation will be assessed centrally by the CALGB. In addition, SNP assessment for FcgRIIa and FcgRIIIa genotype also will be examined to determine if this is associated with toxicity and improved response to the preparative regimen. Other genomic SNPs and genes related to disease resistant features, toxicity assessment, and response may be examined in the future from these patients.

1.5.2 Correlative Science Experimental Plan

1.5.2.1 Immune Reconstitution After Allogeneic SCT

Little is known regarding immune reconstitution following RIC SCT and this issue is complicated by the variable levels of mixed chimerism of the immune cells at varying times post SCT. CLL cells can have a direct effect on healthy allogeneic CD4 and CD8+ T cells [38], so that in patients who are transplanted with bulk disease, or in patients who relapse before DLI, the GVL effect might be dampened by this direct effect on T cells. We shall examine immune cell reconstitution assessing the absolute numbers of CD3, CD8 and CD4/CD25 high T cells, B cells, NK cells and monocytes at baseline, day 30, day 60, day 90, six months, one and two years after SCT. Additional samples will also be analyzed eight weeks after DLI, and at relapse. Immune function will be assessed in those cases in which sufficient cells can be obtained at the same time points; in vitro responses to mitogens and antigens and cytokine responses for Th1 versus Th2 responses will be assessed by ELISA and by ELISPOT. Immune reconstitution will then be correlated with levels of whole blood and T cell chimerism, as well as for presence and level of GVHD and treatment received.

1.5.2.2 Identification of CLL Associated Antigens

A goal of the project is to determine whether there are CLL specific TAAgs that can be a target of the donor immune system in the GVL effect. Of specific interest are antigens that may be broadly expressed by a considerable proportion of patients with CLL. Therefore, we shall examine immune responses against expression libraries prepared from patients in whom purified CLL cells can be obtained. cDNA expression libraries already have been constructed from 12 CLL patients who are representative of different stages, cytogenetic abnormalities and Ig mutation status. We have constructed phage libraries from subtracted cDNA and shall use these also as the basis for screening by SEREX using the sera at different time points after SCT to attempt to identify those Ags that are the target of the GVL immune response. Sera will be screened against the subtracted library to maximize the likelihood that we are identifying CLL specific GVL Ags.

1.5.2.3 Use of Tetramers to Examine T Cell Responses Against Native and Heteroclitic Peptides

Once we have identified potential Ags, we shall demonstrate specificity of response against these antigens using tetramers. Purified HLA-A*0201 peptide monomeric complexes will be synthesized and streptavidin-phycoerythrin (PE) conjugate added at a 1:4 molar ratio. Tetramers will be assembled for Ags identified. Specific T cells will be sorted by FAC analysis and the sorted cells re-stimulated *ex vivo* for subsequent analysis of responses against CLL cells. We shall continue to examine response against Id derived peptides to attempt to confirm and expand previous observations [31].

1.5.2.4 Killing of CLL Cells

The cytolytic activity against patient's CLL cells may be modified by the antigenicity and binding affinity of the antigen, by changes in the T cells and also by intrinsic mechanisms of resistance to T and NK cell mediated killing of the CLL cells. Studies directed at assessing correlations of resistance to killing and clinical and biologic parameters will be limited by the numbers of cases in which patients' CLL cells can be obtained, but we shall attempt to assess killing of CLL cells is correlated with cytogenetics, mutational status, CD38 expression, prior therapy delivered, and whether the patient is deemed chemosensitive or resistant to last chemotherapy before transplant.

1.5.2.5 Interphase Cytogenetics and Stimulated Karyotype

Cryopreserved cells are thawed and treated with 0.075 M KCL for 10 minutes at 37°C. Cells are fixed in 3:1 methanol:acetic acid and slides are prepared. Probes will include 17p13.1 (TP53), 13q14.3(D13S319), 11q22.3 (ATM), 6q23 (CMYB) and centromere 12, all from Vysis (Downers Grove, IL). Other probes for additional abnormalities may be added in the future. FISH is performed following Vysis specifications. The number of signals is evaluated in a field of 200 cells per probe. Standard quality control procedures are used, and a control sample is run concurrently and sensitivity are established as specified (American College of Medical Genetics: Standards and Guidelines for Clinical Genetics Laboratories. 2006 Edition) (http://www.acmg.net/Pages/ACMG_Activitities/stds-2002/e.htm). Similar to this, all baseline samples will be assessed for complex karyotype, and unbalanced translocations using CpG/cytokine stimulated metaphase cytogenetics using an established protocol that will be used by the OSU cytogenetics laboratory. To accomplish this goal, we will perform conventional chromosome studies on B-CLL cells stimulated to undergo mitosis by using CpG oligonucleotide with IL-15 and IL-2. At least 20 metaphase cells will be analyzed for each patient at each study time point. Additional cells will be studies if there is evidence of multiple abnormal clones or subclones. Genomic studies with residual material on assays in the future that correlate with response or toxicity may be performed. These studies will be done by Drs. Nyla Heerema and John Byrd at The Ohio State University.

1.5.2.6 IgVH Gene Mutational Analysis

This analysis will be performed as described by our group [39]. Nucleotide sequences will be aligned to best match in both IgBLAST (http://www.ncbi.nlm.nih.gov/igblast; National Cancer for Biotechnology Information, Bethesda, MD) and in the V Base sequencing directory (http://vbase.mrc-cpe.cam.ac.uk/). IgVH mutated will be defined by 2% or more variance from germ line. These studies will be performed by Drs. Nyla Heerema and John Byrd at The Ohio State University. Other surrogate markers of IgVH mutational status (i.e., ZAP70, CD38 expression or methylation) may be examined with residual material.

1.5.2.7 FcγRIIIa, FcγRIIa, IFN-γ and Other Select Polymorphism Analysis

DNa is extracted using the QIamp kit, according to the manufacturer's instructions (Qiagen, Inc., Valencia, CA). Assessment of IFN-γ, FcγRIIIa, and FcγRIIa single nucleic acid polymorphisms (SNPs) will be performed, and analysis of V/F 158 FcγRIIIa and H/A 131 FcγRIIa conducted as described previously [40, 41]. Other SNPs focused on tumor response or toxicity to

transplant may be examined based on available material. These studies will be done by Dr. John Byrd at The Ohio State University.

1.6 Inclusion of Women and Minorities

Chronic lymphocytic leukemia has a 2:1 male-to-female frequency and is more frequently observed in Caucasians compared to minorities. CALGB 9011 accrued a total of 539 patients of which 32% were female. Race composition of that study was 88% Caucasian, 10% African-American, 1% Hispanic, and 1% other. A similar composition is expected on the present study. Patients who meet the eligibility criteria will be included on this study without regard to gender, race, or ethnicity. Although previous CALGB trial data indicate that women are more likely to respond to treatment than men, gender will be analyzed as a covariate in reporting the results, as will race and ethnicity.

Accrual Targets

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	0	+	1	=	1
Not Hispanic or Latino	24	+	53	=	77
Ethnic Category: Total of all subjects	24	+	54	=	78
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	2	+	6	=	8
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	22	+	48	=	70
Racial Category: Total of all subjects	24	+	54	=	78

2.0 OBJECTIVES

2.1 Primary Objective

The primary endpoint of the study is to determine if this treatment can improve 2-year current progression-free survival (PFS) in the early-disease cohort compared to historical controls. Specifically, we plan to study whether we can achieve 2-year PFS ≥ 70% and to exclude 2-year PFS ≤ 50%.

2.2 Secondary Objectives

2.2.1 To determine whether in the advanced disease cohort we can achieve 2-year current PFS ≥ 50% and to exclude 2-year PFS ≤ 30%.

2.2.2 To assess objective response rate.

2.2.3 To assess the incidence of grade 2-4 and 3-4 acute GVHD.

2.2.4 To assess the incidence of extensive chronic GVHD.

2.2.5 To assess the incidence of TRM at 100 days and one year.

2.2.6 To assess overall survival.

2.2.7 To assess donor chimerism for CD3+ cells at 1 and 2 years after transplantation.

2.2.8 To investigate the presence of donor antigen specific T cell clones before and after withdrawal of immune suppression.

2.2.9 To compare the relapse profiles of the patients with T cell responses against CLL to those whose CLL cells are not reactive.

2.2.10 To prospectively examine the impact of high risk genomic features and immune-based SNPs on response, toxicity, and 2-year PFS to reduced intensity allogeneic stem cell transplant.

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 (BMT CTN)-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:**

- Psychiatric illness which would prevent the patient from giving informed consent.
- 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

Questions concerning patient eligibility should be directed to the CALGB Study Chair.

4.1 Diagnosis of B-CLL or B-SLL according to IWCLL 2008 Criteria [42]

4.1.1 Early Disease Cohort

Patients in the early disease cohort must include <u>one or more</u> of the following:

4.1.1.1 FISH showing deletion 17p in ≥ 20% of cells (either at diagnosis or any time prior to study entry) either alone or in combination with other cytogenetic abnormalities.

4.1.1.2 FISH showing del 11q in ≥ 20% of cells (either at diagnosis or any time prior to study entry) either alone or in combination with other cytogenetic abnormalities, unless the patient has achieved a complete remission by IWCLL 2008 [42] (Appendix I) which includes CT scan, bone marrow morphology and flow cytometry.

4.1.1.3 Failure to achieve a partial response with initial chemotherapy, but with lack of progression. These patients may receive a second therapy to improve their response prior to transplant.

4.1.1.4 In addition, patients in the early disease cohort must have <u>all</u> of the following:

- Received at least 2 cycles of induction therapy. It is expected that most patients will receive at least 4 months of therapy prior to enrollment, but this is not required. Suggested regimens include but are not limited to the following: fludarabine plus rituximab; fludarabine, cyclophosphamide plus rituximab; pentostatin, cyclophosphamide plus rituximab; bendumustine plus rituximab; or alemtuzumab alone or in combination with other agents. Patients may receive no more than 2 different regimens prior to proceeding to transplantation.

- Stable disease or better by the Revised IWCLL 2008 NCI Criteria to most recent therapy (i.e., no prior progression);

- Nodes ≤ 5 cm.

4.1.2 Advanced Disease Cohort

Patients in the advanced disease cohort must include <u>one or more</u> of the following:

4.1.2.1 FISH showing deletion 17p in ≥ 20% of cells (regardless of interval from initial therapy) either alone or in combination with other cytogenetic abnormalities.

4.1.2.2 First progression < 24 months after completing therapy. This includes progression on initial therapy.

4.1.2.3 Second or subsequent progression.

4.1.2.4 In addition, patients in the advanced disease cohort must have all of the following:

- Stable disease or better by the Revised IWCLL 2008 NCI Criteria to their most recent chemotherapy;

- Nodes ≤ 5 cm.

4.2 ECOG performance status 0-2.

4.3 Age ≥ 18 and < 70 years.

4.4 At least 4 weeks after day 1 of the last cycle of cytotoxic chemotherapy, or alemtuzumab.

4.5 No HIV infection. Allogeneic transplantation in the HIV patient population is not well-defined and there are likely to be requirements for concomitant anti-HIV therapy and anti-GVHD therapy that would create potentially dangerous pharmacokinetic interactions among the different agents that could constrain therapeutic options for controlling both HIV and GVHD.

4.6 No Hepatitis B sAg, anti-HBc or HCV.

4.7 DLCO ≥ 40% predicted.

4.8 LVEF by ECHO or MUGA ≥ 30%.

4.9 No uncontrolled diabetes mellitus or active uncontrolled serious infections.

4.10 Non-pregnant and non-nursing. Treatment under this protocol would expose a fetus to significant risks. Women of childbearing potential should have a negative pregnancy test prior to study entry. Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include oral contraceptives, implantable hormonal contraceptives (Norplant®), or double barrier method (diaphragm plus condom).

4.11 No history of Richter's transformation.

4.12 Initial Required Laboratory Values

Serum Creatinine	< 2 mg/dL
Calculated Creatinine Clearance	≥ 40 mL/min
AST	< 3 x ULN
Total Bilirubin	< 2 mg/dL (except for Gilbert's syndrome)

5.0 DONOR ELIGIBILITY

5.1 Donors may be either a 6/6 HLA-matched <u>related</u> donor by low-resolution typing at HLA A, B, C, DR.

5.2 Donors may be an 8/8 HLA-matched <u>unrelated</u> donor at HLA A, B, C, DR. Unrelated donors will be analyzed by molecular typing at both HLA Class I and Class II (A, B, C, DR loci).

5.3 Syngeneic donors are not eligible.

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

5.5 There will be no donor age restriction.

6.0 REGISTRATION

6.1 Registration Requirements

6.1.1 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 a consent form is required.

6.1.2 CALGB-Approved or BMT CTN-Approved Transplant Institution

CALGB institutions must have fulfilled their cooperative group institutional transplant requirements. CALGB requirements include either FACT accreditation or approval by the CALGB Transplant Committee.

BMT CTN affiliated institutions must have fulfilled the BMT CTN regulatory requirements, including FACT accreditation, CAP accreditation, CLIA accreditation, Medical License of PI, Financial Disclosure, and a copy of the IRB-approved consent document and IRB approval letter. Regulatory documents should be submitted to the BMT Central Office at the following address:

ATTN.: Cathy Gurgol
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850
Phone: (301) 251-1161 x2828
Fax: (240) 306-0963
email: cgurgol@emmes.com

6.2 CALGB Registration

6.2.1 CALGB 20802 Pre-registration

There is one correlative science companion study to CALGB 100701, CALGB 20802 (See Sections 6.2.3 and 7.3). At the time of the first sample collection, patients may be pre-registered to the correlative science study CALGB 20802. This is an optional pre-registration step for patients who consent to CALGB 20802 (Model Consent Question #1) in order to allow for submission of the prior to treatment samples described in Section 7.3.1.

6.2.2 CALGB Registration Procedures

This study uses the CALGB Web-based Patient Registration system. Registration will be accepted only through CALGB Main Member Institutions, at-large members, selected affiliate institutions and CCOPs using the Web-based Patient Registration system. Registration must occur prior to the initiation of therapy.

Confirm eligibility criteria (Section 4.0). Complete the Registration Worksheet. Access the Web-based Patient Registration system via the Patient Registration tab on the CALGB Member Website at www.calgb.org. If the study does not appear on the list of studies in the Patient Registration system, the registration must be performed by the CALGB Registrar via phone or fax. If the registering CRA requires assistance, he/she may consult the on-line help file at the bottom of the screen or call the IS Help Desk at 1-888-44CALGB. If further assistance is required, the registering CRA may call the CALGB Registrar (919)-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time. Enter the following information:

CALGB patient ID #, if applicable
Study
Name of group (CALGB)
Name of institution where patient is being treated
Name of treating physician
Name of person in contact with the patient record (responsible contact)
Protocol IRB approval date
Date of signed consent
Treatment Start Date (if applicable)
Date [of] HIPAA authorization signed by the patient
Patient's initials (last initial, first initial, middle initial)
Patient's Social Security #, date of birth, hospital ID #, and survival status
Patient's gender
Patient's race
Patient's ethnicity
ECOG performance status
Patient's height (cm) and weight (kg) (if applicable)
Type of insurance (Method of Payment)
Patient's postal code
Disease, type and stage, if applicable
Eligibility criteria met (no, yes)

Companion studies patient has consented

When the patient is registered, a CALGB patient identification number will be generated. Please write the number in your records. Registration to any mandatory or optional companion studies will be done at the same time as registration to the treatment study. Registration to both treatment and companion studies will not be completed if eligibility requirements are not met for all selected trials (treatment and companions).

The Main Member Institution and registering institution will receive a Confirmation of Registration. Please check both confirmations for errors. Submit corrections in writing to the data coordinator at the CALGB Statistical Center, Data Operations, 2424 Erwin Rd, Ste 802 Hock Plaza, Durham, NC 27705, or fax to 919-668-9397.

6.2.3 Registration to Companion Studies

Within CALGB 100701, there is one substudy. This embedded companion must be offered to patients enrolled on CALGB 100701, although patients may opt not to participate in CALGB 20802 (see below). The substudy included within CALGB 100701 is:

- Correlative Science in CALGB 100701 (CALGB 20802). The rationale for performing this correlative science substudy is discussed in Section 1.5.
- Patients may be pre-registered to CALGB 20802 at the time of the consent in order to generate a patient ID with which to submit the initial correlative science samples (see Section 7.3).

6.3 BMT CTN Registration

6.3.1 BMT CTN Registration Procedures

BMT CTN centers will register the patient first in AdvantageEDC, the BMT CTN electronic data capture system. AdvantageEDC automatically notifies the BMT CTN Data Coordinating Center (DCC) of the registration. The BMT CTN DCC will then register the patient in the CALGB Web-based system. The BMT CTN Office will complete the registration process using the CALGB Web-based system and will obtain the CALGB patient ID number. Patients must be registered in the AdvantageEDC system prior to initiation of treatment.

All correspondence with CALGB must include the CALGB patient ID number.

6.3.2 Registration to Companion Studies

Within CALGB 100701, there is one substudy. This embedded companion must be offered to patients enrolled on CALGB 100701, although patients may opt not to participate in CALGB 20802 (see below). The substudy included within CALGB 100701 is:

- Correlative Science in CALGB 100701 (CALGB 20802). The rationale for performing this correlative science substudy is discussed in Section 1.5.

If a patient consents to Question #1 of the Recipient Model Consent Form (Section 19.0), they may be registered to CALGB 20802.

7.0 CENTRAL FISH REVIEW, DATA SUBMISSION AND CORRELATIVE SCIENCE SAMPLE SUBMISSION

7.1 Central FISH Review

The FISH results obtained at diagnosis, or at any time prior to entry on this study, will be reviewed centrally. Institutions must submit images of 2 or more abnormal cells per clone (or 2 normal cells in the case of a normal analysis) for central FISH review for 17p13.1 (TP53), 11q22.3 (ATM), and 13q14.3 (D13S319). These should be submitted together with Form I-057 (CALGB 100701 Central FISH Image and Pathology Submission Form) within 28 days following patient registration. If a site is unable to submit the images within 28 days of patient registration, they should

contact the cytogenetics lab at the contact information provided below. Submission procedures are as follows:

Send electronic FISH images (.jpg or .tif) via secure email to calgbcytogenetics@osumc.edu (preferred method). **Do not submit FISH images over non-secure email.** If a site has not previously used the CALGB secure email, they are to send an email request to calgbcytogenetics@osumc.edu, with SECURE EMAIL ACCOUNT REQUEST in the subject line. The email sent in response will provide instructions to set up a secure email account. Once the secure email account is set up, please submit the FISH images. If a site is unable to submit the FISH images electronically, sites may send electronic images on a CD or hard copy images to the mailing address listed below.

Send saved or scanned PDF version of Form I-057 (see the forms table in Section 7.2) via secure email to calgbcytogenetics@osumc.edu. The form may also be sent via fax to 614-293-3575, as PDF files by CD, or as hard copies via US Mail or courier service.

CALGB Cytogenetics Office
Tzagournis Medical Research Facility
Room 360
Ohio State University Medical Center
420 W. 12th Avenue
Columbus, OH 43210-2208
Tel: 614-293-2542
Fax: 614-293-3575
calgbcytogenetics@osumc.edu

Questions concerning completion of these requirements may be directed to the CALGB Cytogenetics Office.

If a site is not able to submit images of 2 cells for central FISH review, but the patient meets all of the other eligibility criteria, they may still be enrolled on study. In this circumstance, please contact the Study Chair.

7.2 Data Submission

CALGB and BMT CTN institutions will submit forms to the CALGB Statistical Center, Data Operations in compliance with the data submission schedule below. There are three options for submitting forms that use the Teleform barcode and cornerstones:

- the preferred method is to submit the forms electronically using the “Submit to CALGB” button at the bottom of the last page of each form. Forms submitted electronically should not be submitted by fax or e-mail.
- the forms may be faxed to the Statistical Center, Data Operations at 919-416-4990. 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 Statistical Center, Data Operations, 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.

Amended data and supporting documentation (e.g., reports or flow sheets) must be submitted by fax (919-416-4990) or mail (CALGB Statistical Center, Data Operations, Hock Plaza, Suite 802, 2424 Erwin Road, Durham, NC 27705).

Form†		Submission Schedule
Baseline		
C-1806	CALGB 100701 On-Study Form	
C-1887	HLA Typing Form	
C-970	CALGB Peripheral Blood and Bone Marrow Form	
C-1885	Leukemia Pathology Form- Cytogenetics	Within one month of registration.
C-1916	CALGB 100701 Measurement Form	
	Reports*	
I-057	CALGB 100701 Central FISH Image and Pathology Submission Form	Submit to the CALGB Cytogenetics Lab with cell images for FISH analysis (see Section 7.1).
Allogeneic Peripheral Blood Stem Cell Infusions		
C-1886	Donor Cell Product Form	Submit at Days-5 through +90. *If a patient does not begin Maintenance Therapy, submit C-1808, C-1807, and C-664 until and when patient starts non-protocol therapy.*
C-1807	CALGB 100701 Follow-up Form	
C-1808	CALGB 100701 Adverse Event Form	
C-1924	CALGB 100701 Chimerism Results Form	
	Chimerism Reports	
Maintenance Therapy		
C-1808	CALGB 100701 Adverse Event Form	Submit q 3 months for one year post transplant.
C-1807	CALGB 100701 Follow-up Form	
C-1924	CALGB 100701 Chimerism Results Form£	
	Chimerism Reports	
C-970	Peripheral Blood and Bone Marrow Form	
C-1916	CALGB 100701 Measurement Form	Submit at 3 and 12 months post Day 0 of transplant
	Reports*	
Follow-Up (Post-Treatment)		
C-1807	CALGB 100701 Follow-up Form	Submit every 3 months during second post-transplant year.
C-1808	CALGB 100701 Adverse Event Form	
C-970	Peripheral Blood and Bone Marrow Form	Submit at month 24 post Day 0 of transplant, and at time of progression.
C-1916	CALGB 100701 Measurement Form	
C-400	CALGB: Long-Term Follow-Up Form	Submit every 6 months post Month 24 for a maximum of 5 years from study entry, and at time of progression.
Other Forms		
C-300	Off Treatment Form	At end of all protocol treatment.
C-664	Infectious Complications Form	Submit only in the event of infection.
C-1001	New Malignancy Form	At occurrence of new malignancy.
C-1820	Adverse Events Addendum Form	Complete if additional space is needed to report other adverse events. See form for instructions.
C-113	CALGB Notification of Death Form	At time of death‡.
C-1886	Donor Cell Product Form	Submit only if patient receives DLI.

* As *they become available* legible copies of all institutional pathology, cytochemistry, immunophenotyping, and cytogenetic reports used for patient registration must be submitted to the CALGB Statistical Center, Data Operations. Include the CALGB patient ID numbers on all report forms.

† Use the CALGB Remarks Addenda (C-260) if additional comments are necessary or additional writing space is needed.

ǂ All deaths within two years following protocol treatment that are not due to disease progression should be reported as adverse events.
£ Form C-1924 and chimerism results are not required at Month 9.

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

Common Terminology Criteria for Adverse Events (CTCAE): This study will utilize the Common Terminology Criteria for Adverse Events version 4.0 for toxicity and adverse event reporting.

7.3 Interphase Cytogenetics and Stimulated Karyotype, IgVH Mutational Analysis, and FcR Polymorphism, Immune Reconstitution, CLL Associated Antigen Identification, and T-Cell Response Assessment Correlative Science Sample Submission (CALGB 20802)

7.3.1 Sample Procurement

- **Transplant Recipient**

  In patients who consent (Model Consent Question #1), three additional samples are to be collected prior to treatment:

  - 18 mL bone marrow aspirate in green top [heparinized, preferably lithium heparin] tubes;
  - 10 mL peripheral blood in a lavender top (EDTA) tube;
  - if a patient has circulating cells, submit an additional 10 mL peripheral blood in a green top [heparinized] tube);

  Collect 20 mL peripheral blood in four 6 mL green top (heparinized) tubes and 10 mL peripheral blood in a red top (no anticoagulant) tube at each of the following time points below:

  - One month post-transplant;
  - Two months post-transplant;
  - Three months post-transplant;
  - Six months post-transplant;
  - Twelve months post-transplant;
  - Twenty-four months post-transplant;
  - Eight weeks after each occurrence of donor lymphocyte infusions (DLI);
  - At time of documented clinical relapse.
  - If diagnostic bone marrow and peripheral blood specimens are available, please submit specimens as indicated above. If patients were enrolled previously on CALGB 10404 it would not be required to submit additional specimens, as diagnostic specimens would be available for research.

- **Transplant Donors**

  In related donors who consent (donor model consent question #1), collect 20 mL of peripheral blood in four 6 mL green top (heparinized) tubes along with 10 mL of peripheral blood in a red top (no anticoagulant) tube prior to treatment.

7.3.2 Sample Submission

Label the tubes with the CALGB study number, CALGB patient ID, patient initials, the date of collection, source of material, and the sample collection period.

All submitted specimens must be labeled with the protocol number CALGB 20802, CALGB patient number, patient's initials, and date and type of specimen collected (e.g., serum, whole blood).

In the red top and lavender top lubes, ship the specimens cold (refrigerator temperature). In the green top tubes, ship the specimens at ambient temperature. If it is not possible to ship at two separate temperatures, then all tubes may be shipped cold. Frozen cold packs should NOT be used.

Specimens for patients pre-registered and registered to this study must be logged and shipped using the online CALGB Specimen Tracking System. All institutions may access this system via the CALGB Web site, http://www.calgb.org.

A copy of the Shipment Packing Slip produced by the CALGB Specimen Tracking System must be printed and placed in the shipment with the specimens.

USE OF THE SPECIMEN TRACKING SYSTEM IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

For procedural help in logging and shipping specimens, please refer to the Specimen Tracking System User Guide, which can be accessed via the Help link within the Specimen Tracking System.

To report technical problems with the CALGB Specimen Tracking System, such as login issues or application errors, and/or for further assistance using the application, please contact the CALGB Help Desk at 877-44CALGB or calgb-support@calgb.duhs.duke.edu.

Please be sure to use a method of shipping that is secure and traceable. **Samples must be shipped on the same day they are obtained. If holiday schedules prevent same day shipment, please contact the Leukemia Tissue Bank Lab Supervisor at 614-292-5888 for sample shipment instructions.** Send bone marrow blood samples at ambient temperatures, Monday through Friday, via overnight carrier for next day (**check AM**) delivery to:

CALGB Leukemia Tissue Bank
Michael Caligiuri, M.D.
The Arthur G. James Cancer Center Hospital and Research Institute
Attn.: CALGB 20802
300 W. 10th Avenue, Suite 519
Columbus, OH 43210
Tel: (614) 293-7521
Fax: (614) 293-7522

Note: If specimen is sent on Friday, CHECK SATURDAY DELIVERY on the FEDERAL EXPRESS INVOICE.

8.0 REQUIRED DATA

Guidelines For Pre-Study Testing

To be completed within 16 DAYS before registration:

- All bloodwork (except HLA typing)
- History and physical

To be completed within 28 DAYS before registration:

- Bone marrow examinations
- 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., ECHO, MUGA
- Any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement
- Pulmonary function tests (DLCO corrected for Hgb)

Tests & Observations	**Prior to Regis-tration**	**Prior to Rituximab Maintenance Therapy**	**During Rituximab Maintenance Therapy† (Months 3, 6, 9, 12)††**	**Post Treatment‡**
History & Progress Notes	X	X	X	X
Physical Examination	X	X	X	X
Height	X			
Weight/BSA	X	X	X	X
Performance Status	X	X	X	X
Tumor Measurements£	X	X	X	X
GVHD Assessment		X	X	X
Toxicity Assessment		X	X	X
Laboratory Studies				
CBC with Diff, Platelets	X	X	X	X
Serum Creatinine, CrCL calculated	X	X	Cr only	Cr only
AST, Alk.Phos., Bilirubin	X	X	X	X
LDH	X	X	X	X
PFTs (DLCO corrected for Hgb)	X			
LVEF by ECHO or MUGA	X			
SPEP	X	X		
Hep B sAB, sAg, core Ab, Hep C Ab, HIV	X			
Serum or urine HCG	X			
DAT`	X			
Staging				
Flow Cytometry**	X	A	A	A
Chest/Abd/Pelvis CT	X	B	B	B
Chimerism		C	C	
Bone marrow asp & bx	X	A	A	A
FISH bone marrow (probes17p, 11q, 13q)	X	A	A	A

***** Within 2 weeks prior to initiation of maintenance therapy.

† Prior to each rituximab dose (months 3, 6, 9, and 12) regardless of whether dose is administered.

†† Rituximab maintenance visits may be moved up or back by as many as two weeks to accommodate patient/clinic scheduling.

‡ Q3 months during second post-transplant year, then q 6 months for a maximum of 5 years from study entry. Post treatment follow-up visits may be moved up or back by as many as two weeks to accommodate patient/clinic scheduling.

** Flow cytometry (bone marrow) for diagnosis must include CD5, CD19, CD23.

£ Including lymph nodes and spleen by physical exam.

A Bone marrow examinations at 3, 12, 24 months post Day 0 of transplant (to include FISH and flow cytometry).

B CT scans at 3, 12, and 24 months post Day 0 of transplant.

C Peripheral blood whole cell and T cell institutional chimerism to be performed at 1, 3, 6, and 12 months post Day 0 of transplant. Submit chimerism reports to the CALGB Statistical Center, Data Operations as per Section 7.1.

9.0 TREATMENT PLAN

9.1 Mobilization and Apheresis of Donor Peripheral Blood Stem Cells

- Only peripheral blood grafts will be allowed. Bone marrow grafts will not be allowed.
- Any mobilization regimen will be allowed. Patients must be registered prior to initiation of preparative regimen.
- A minimum CD34+ cell dose of 2 x 10^6/kg recipient weight should be collected with a goal of collecting ≥ 5 x 10^6/kg. Cells may be collected either prior to transplant and cryopreserved or collected fresh according to institutional practice. It is suggested that the infused cell dose be < 8 x 10^6/kg but there will be no specified cap on the cell dose.

9.2 Preparative Regimen

Two different preparative regimens will be allowed. In any patient, institutions may elect to use **EITHER** preparative regimen 1 (Section 9.2.1) **OR** preparative regimen 2 (Section 9.2.2). Chemotherapy doses for both regimens will be based on actual weight unless patient weight is ≥ 150% of ideal body weight (see Appendix I) in which case a corrected weight will be calculated as ideal weight + 25% (actual weight - ideal weight).

9.2.1 Preparative Regimen 1 (Fludarabine + Busulfan + Rituximab)

GVHD prophylaxis regimen 1 (Section 9.3.1) or prophylaxis regimen 2 (Section 9.3.2) should be used in conjunction with preparative regimen 1.

9.2.1.1 Fludarabine 30 mg/m^2/day IV infusion over 30 minutes on Days -5, -4, -3, and -2.

9.2.1.2 Busulfan 0.8 mg/kg/day IV infusion over 3 hours on Days -5, -4, -3, and -2.

9.2.1.3 Rituximab 500 mg/m^2/day IV infusion on Days -7, -1, +7, and +14 at an infusion rate and with pre-treatment according to institutional preferences.

9.2.1.4 Day 0 is the last day of the first stem cell infusion if more than 1 day is required.

9.2.2 Preparative Regimen 2 (Fludarabine + Cyclophosphamide rATG [MUD ONLY] + Rituximab)

GVHD prophylaxis regimen 2 (Section 9.3.2) should be used in conjunction with preparative regimen 2.

9.2.2.1 Fludarabine 30 mg/m^2/day IV over 30 minutes on Days -5, -4, -3, and -2.

9.2.2.2 Cyclophosphamide 1 g/m^2/day IV over 1-2 hours on Days -5, -4, and -3.

9.2.2.3 Rabbit Antithymocyte Globulin (rATG) [<u>Unrelated Donors ONLY</u>]

For each rATG infusion, patients must be premedicated with acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO/IV, and methyprednisolone 1

mg/kg at initiation of rATG infusion and again midway through rATG infusion.

On Day -6, rATG 1.5 mg/kg will be administered by IV infusion. The first dose should be infused over at least six hours and subsequent doses may be infused over 4 hours.

On Day -5, rATG 2.0 mg/kg will be administered by IV infusion.

On Day -4, rATG 2.5 mg/kg will be administered by IV infusion.

Total dose is 6 mg/kg.

9.2.2.4 Rituximab 500 mg/m^2/day IV on Days -7, -1, +7, and +14 at an infusion rate and with pre-treatment according to institutional preferences.

9.3 GVHD prophylaxis

Two regimens for GVH prophylaxis will be allowed. However, GVHD prophylaxis regimen 1 (tacrolimus, sirolimus, methotrexate) may be used **ONLY** in conjunction with preparative regimen 1 (fludarabine, busulfan, rituximab). Prophylaxis regimen 2 may be used with either preparative regimen 1 or preparative regimen 2.

9.3.1 GVHD Prophylaxis Regimen 1 (Tacrolimus, Sirolimus, Methotrexate)

NOTE: This GVH prophylaxis regimen should be used ONLY in patients who have received preparative regimen 1.

- **Tacrolimus** starting Day -2 either orally or IV to achieve a target serum level of 5-10 ng/mL.
- **Sirolimus** will be given in a loading dose of 12 mg PO on Day -2, followed by an oral dose of 4 mg/day. Subsequent dosing will be based on clinical toxicity, GVHD concurrent medications, medical conditions, prior drug levels, drug-drug interactions and blood levels with a target of 3-12 ng/mL. For levels < 2 ng/mL, a dose increase of 25% is recommended. For levels > 12 ng/mL, a dose decrease of 25% is recommended. Dose may be rounded to the nearest 1 mg dose. Levels will be checked weekly for the first month and then monthly thereafter. The dose will be replaced if the patient vomits within 15 minutes of taking a dose.
- **Methotrexate** 5 mg/m^2/day IV will be given on Days +1, +3, +6. Methotrexate doses may be adjusted or leucovorin added according to institutional guidelines.
- **Immunosuppression Tapering**

  In the absence of graft versus host disease, both tacrolimus and sirolimus should be tapered by 1/3 between Days +60 and +90. Thereafter, both agents should be tapered to zero between Days +150 and +180, as clinically permissible.

9.3.2 GVHD Prophylaxis Regimen 2 (Tacrolimus + Methotrexate)

Prophylaxis regimen 2 may be used with either preparative regimen 1 or preparative regimen 2.

- **Tacrolimus** starting on Day -2 either orally or IV to achieve a target serum level of 5-10 ng/mL.

- **Methotrexate** 5 mg/m^2/day IV will be given on Days + 1, +3, +6 and +11.
- In the absence of graft versus hose disease, tacrolimus should be tapered by 1/3 between Days +60 and +90. Thereafter, both agents should be tapered to zero between Days +150 and +180, as clinically permissible.

9.4 Allogeneic Peripheral Blood Stem Cell (PBSC) Infusions

Donor PBSC will be infused intravenously beginning on Day 0. A minimum cell dose of ≥ 2 x 10^6/kg recipient weight should be infused. There will not be a specified cap on the infused CD34+ cell dose, but it is suggested that it be < 8 x 10^6/kg. Infused cells may be either fresh or previously cryopreserved. Cells should be infused according to institutional standards.

9.5 Supportive Care

9.5.1 In conjunction with chemotherapy, patients will receive pre-hydration and intravenous fluids and/or diuretics as needed. Antiemetics may be given as per institutional guidelines.

9.5.2 Antiviral and antibacterial prophylaxis and treatment should follow conventional post-transplant guidelines and institutional guidelines.

9.6 Rituximab Maintenance Therapy

Rituximab 500 mg/m^2/day will be administered by IV infusion at months 3, 6, 9, and 12 post Day 0 of transplant. Rituximab will be given at an infusion rate and with pre-treatment according to institutional preferences. The rituximab infusion may be moved up or back by as many as two weeks to accommodate patient/clinic scheduling. Rituximab dose will be based on actual weight unless patient weight is ≥150% of ideal body weight (see Appendix II) in which case a corrected weight will be calculated as ideal weight + 25% (actual weight - ideal weight).

9.7 Donor Lymphocyte Infusion (DLI)

9.7.1 The use of DLI will not be mandated, but may be a treatment option under certain situations.

9.7.2 DLI may be given ONLY for disease progression but NOT for either stable disease or persistent disease.

9.7.3 In some circumstances the use of DLI will be permitted for falling donor CD3 chimerism. These cases must be discussed with the Study Chair (or his designee) to allow DLI. It is suggested that criteria for the use of DLI in response to poor chimerism be donor CD3 < 40% on two occasions but this is not required.

9.7.4 Patients must be off immunosuppression for ≥ 30 days and be without active GVHD.

9.7.5 Subsequent DLI infusions will be given no sooner than 8 weeks apart if no GVHD develops.

9.7.6 The initial DLI doses will be suggested but not mandated. It is suggested that the initial DLI doses will be 1 x 10^7/kg (related donors) and 5 x 10^6/kg (unrelated donors).

9.7.7 It is suggested that the second DLI dose, to be given no sooner than 8 weeks from the initial dose, be 5 x 10^7/kg (related donors) and 1 x 10^7/kg (unrelated donors).

10.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

10.1 Keystone Convention for grading GVHD [43]

Organ Grade	Skin*	Bilirubin (mg/dL)	Gut Changes (diarrhea [mL/day])
1	Rash < 25%	2.0 - < 3.0	> 500 - 999 or biopsy-proven upper GI involvement
2	Rash 25-50%	3.1 - 6	≥ 1000 - < 1499
3	Rash > 50%	6.1 - 15	≥ 1500
4	Generalized erythroderma with bullae	> 15	Severe abdominal pain with or without ileus

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

* Use "rule of nines" to determine body surface area

10.2 Clinical Grading of Chronic GVHD

10.2.1 Limited Chronic GVHD:

1. Localized skin involvement,

   and/or

2. Hepatic dysfunction due to chronic GVHD.

10.2.2 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.

10.3 Rituximab Maintenance Therapy Dose Modifications

Prior to rituximab maintenance therapy, if ANC is < 1000/μL, hold rituximab dose until ANC ≥ 1000/μL. If after two weeks, ANC continues to be < 1000/μL, then the scheduled rituximab dose should be skipped.

10.4 Fludarabine Dose Modification

Local institutional standards may be followed for fludarabine dose reductions in patients with minimal CrCl levels.

11.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

11.1 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.

11.2 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.

11.3 The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

11.4 Institutional practice related to preparation and administration of study drugs may be used in place of protocol instructions. Institutions with differing practice should contact the study chair for approval.

11.5 Fludarabine Monophosphate [Fludara; Berlex laboratories]

AVAILABILITY

Fludarabine monophosphate is commercially available as a sterile powder in 50 mg vials containing 50 mg of mannitol and sodium hydroxide to adjust the pH to 7.7. Please refer to the agent's package insert for additional information.

STORAGE & STABILITY

Intact vials should be stored under refrigeration (2°-8°C). Reconstituted fludarabine phosphate contains no antimicrobial preservative and thus should be used within 24 hours of reconstitution. Solutions diluted in D_5W or NS are stable for 48 hours at room temperature or under refrigeration.

PREPARATION

Vials of fludarabine are reconstituted with 2 mL of sterile water for injection to yield a 25 mg/mL solution. The product should be further diluted for intravenous administration in 100 or 125 dextrose or in 0.9% saline.

ADMINISTRATION

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

TOXICITY

Myelosuppression (dose limiting toxicity), fever, nausea and/or vomiting, skin rashes, myalgia, fatigue, autoimmune hemolytic anemia (may be life-threatening), and pulmonary toxicity (both pneumonia and pulmonary hypersensitivity reactions have been reported; fatal pulmonary toxicity has been described, especially when fludarabine was used in combination with pentostatin). Severe or fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status has been described primarily after high doses of fludarabine monophosphate, or at usual doses (25-30 mg/m^2) in elderly patients. Very rarely described complications include transfusion-associated graft versus host disease, thrombotic thrombocytopenic

purpura, and liver failure. Tumor lysis syndrome has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed. Please refer to the package insert for additional information.

DRUG INTERACTIONS

USE OF FLUDARABINE WITH CORTICOSTEROIDS SHOULD BE AVOIDED DUE TO A SIGNIFICANT INCREASE IN OPPORTUNISTIC INFECTIONS.

11.6 **Rituximab** (IDEC-C2B8, Rituxan®)

AVAILABILITY

Rituximab will be provided, free of charge, by Genentech and distributed through Biologics, Inc. Rituximab will be supplied as 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL.

Please refer to the agent's package insert for additional storage, stability, preparation, and toxicity information.

Ordering

Institutions will complete the Drug Order Request Form available on the CALGB 100701 study Web page under "Supplemental Materials." The form will be faxed (or emailed, if applicable) to Biologics Inc:

Biologics Inc.
120 Weston Oaks Court
Cary, NC 27513
Tel: 800-850-4306 Extension 106
Fax: 919-256-0794
Attn: Karl Buer, CPhT
clinicaltrials@biologicstoday.com

DRUG ACCOUNTABILITY & DISPOSITION

Institutions should document drug accountability using the NCI Drug Accountability Record From (DARF).

At the end of the study unused rituximab should be destroyed per institutional processes. Drug destruction should be recorded on the DARF.

STORAGE & STABILITY

Intact vials should be stored under refrigeration (2°-8°C). Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

PREPARATION

The desired dose of rituximab should be diluted in 0.9% NaCl or D_5W to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

ADMINISTRATION

See protocol treatment section for specific administration instructions.

TOXICITY

The most severe serious adverse events associated with rituximab include severe infusion reactions, tumor lysis syndrome, and severe mucocutaneous reactions.

Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab. If a reaction occurs, the infusion rate should be stopped until the symptoms resolve, and then restarted at a 50% slower rate. Because severe infusion reactions have been noted more frequently in patients with high leukocyte counts, such patients should be observed more closely.

Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells (≥ 25,000/μL). In this study, allopurinol will be administered prophylactically with the first induction cycle. Use of allopurinol with subsequent cycles is at the discretion of the treating physician.

Severe mucocutaneous reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills, and dyspnea. The mechanism of rituximab infusion reactions is thought to be secondary to release of cytokines. Infusions may be stopped until symptoms resolve. Refer to the package insert for additional information. Pretreatment with acetaminophen and diphenhydramine before each dose of rituximab may minimize the likelihood/severity of infusion reactions.

Recent reports describe hepatitis B reactivation with fulminant hepatitis, hepatic failure, and death in some patients with hematologic malignancies treated with rituximab. The majority of these patients receive rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately one month after the last dose.

Exacerbation or reactivation of other viral infections also has been reported with rituximab. Recent reports describe the JC virus reactivation leading to progressive multifocal leukoencephalopathy (PML) in patients who were receiving rituximab. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for PML.

A report in the literature described an increase in fatal infection in HIV-related lymphoma patients when rituximab was used in combination with CHOP chemotherapy, as compared to CHOP alone. Patient with HIV infection are not eligible for entry on this research study.

In patients with Waldenström's macroglobulinemia, following initiation of rituximab, transient increases in serum IgM levels have been observed which may result in hyperviscosity syndrome requiring plasmapheresis.

11.7 **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 1 mL 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 μg/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 mg/mL 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 cryptococcemia (5%). The source of bloodstream infection was primarily intravascular catheter, accounting for 39% of cases.

11.8 Sirolimus

AVAILABILITY

Sirolimus is commercially available either as a 1 mg or 2 mg tablet, or as an oral solution in 60 mL bottles at a concentration of 1 mg/mL

STORAGE & STABILITY

Oral solution should be stored protected from light and refrigerated at 2°C - 8°C (36°F to 46°F). Once the bottle is opened, contents should be used within one month.

Tablets should be stored at 20°C - 25°C (68°F - 77°F), and should be protected from light.

ADMINISTRATION

Orally.

TOXICITY

Abdominal pain, asthenia, back pain, chest pain, fever, headache, pain, hypertension, constipation, diarrhea, dyspepsia, nausea, vomiting, anemia, leukopenia, thrombocytopenia, increased levels of creatinine, edema, hypercholesterolemia, hyperkalemia, hyperlipemia, hypokalemia, hypophosphatemia, peripheral edema, weight gain, arthralgia, insomnia, tremor, dyspnea, pharyngitis, upper respiratory infection, acne, rash, urinary tract infection.

11.9 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 D_5W.

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; pruritus, 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.

11.10 **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 3-hour infusion on Days -5, -4, -3, and -2.

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 regimens which may include narcotic analgesic and potentially parenteral nutrition.

2. Painful desquamation may require local care and narcotic analgesics.

11.11 Cyclophosphamide (Cytoxan®; CTX; CPA; Endoxan®; Neosar®; Cytoxan Lyophilized®)

AVAILABILITY

Commercially available in 100 mg/10 mL, 200 mg/20 mL, 500 mg/30 mL, or in a powder for injection in 100 mg, 200 mg, 500 mg, 1 gram, and 2 gram vials.

PREPARATION

Reconstitute 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials with 5, 10, 25, 50, or 100 mL of SWI or NS to give a final concentration of 20 mg/mL.

Vigorous shaking, gentle warming may be necessary for non–lyophilized preparation.

Bacteriostatic water for injection (paraben preserved only) may be used; benzyl alcohol derivatives may NOT be used. Further dilute in 100 - 250 ml of D_5W or NS for IV infusion.

ADMINISTRATION

Dissolved in 250 mL D_5W.

Appropriate antiemetic therapy will be used. Patients must be adequately hydrated before, during, and after administration of cyclophosphamide.

STORAGE & STABILITY

Solutions reconstituted with SWI or bacteriostatic water are stable for 24 hours at room temperature and 6 days if refrigerated.

TOXICITY

Myelosuppression: leukopenia (nadir 8-14 days), thrombocytopenia. Acute sterile hemorrhagic cystitis (patients must be well-hydrated before, during, and after treatment and have adequate renal function). Syndrome of inappropriate antidiuretic hormone (SIADH). Bladder carcinomas and cellular dysplasias, alopecia (50%). GI: anorexia, nausea, vomiting, diarrhea. Sterile phlebitis. Rare pulmonary toxicity. Gonadal abnormalities, teratogenicity. With too rapid IV push, oropharyngeal tingling, “metallic” taste, headache, urticaria, and facial flushing can occur. With high doses, cardiac toxicity.

11.12 Antithymocyte Globulin (Rabbit)

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

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 calculated 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

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

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.

12.0 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.

13.0 POST TRANSPLANT CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

Criteria for response will utilize the IWCLL 2008 Criteria [42] for response which includes clinical, hematologic, and now marrow features from the initial 1996 NCI guidelines [44]. Because of the confounding effect of complications of allogeneic transplant on peripheral blood counts, normal blood counts will not be required to fulfill the criteria for complete remission.

13.1 Response Criteria

13.1.1 Complete response: Requires all of the following for a period of at least three months from completion of therapy:

- Absence of lymphadenopathy > 1.5 cm on physical exam and CT scan;
- No hepatomegaly or splenomegaly on physical exam;
- No clonal B-cells in the blood by flow cytometry;
- No clonal B-cells in the bone marrow aspirate. Bone marrow aspirate and biopsy must have < 30% of nucleated cells being lymphocytes. Flow cytometry/immunohistochemistry should be performed on bone marrow. Lymphoid nodules may be present but must be T-cell in origin. If these are demonstrated to be clonal B-cells, patients should be considered a partial response. Additionally, if bone marrow is positive by two color flow cytometry for CLL cells it should be considered a partial response.

13.1.2 Partial Response: Requires a ≥ 50% decrease in peripheral lymphocyte count from pre-treatment value, ≥ 50% reduction in lymphadenopathy of as many as 6 measurable lymph nodes, and/or ≥ 50% reduction in splenomegaly/hepatomegaly for a period of at least two months. Patients may have bone marrow lymphoid nodules of B-cell origin.

13.1.3 Progressive Disease: Characterized by any one of the following events:

- ≥ 50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥ 2 cm); appearance of new palpable lymph nodes.
- ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- > 50% increase in peripheral blood lymphocytes with an absolute increase > 5000/μL.
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes).

13.1.4 Stable Disease: Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

14.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

14.1 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.

14.2 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.

15.0 STATISTICAL CONSIDERATIONS

The primary clinical endpoint of interest for both the early- and advanced-diseased cohorts will be progression-free survival (PFS) as defined in Section 15.1. Death due to any cause will be considered an event. Furthermore, a progression that is brought under control by either the withdrawal of immunosuppression or the use of DLI is nullified, and the patient can be counted as being progression-free if this response is maintained. Disease progressions that are treated with other non-protocol specified therapy will be counted as progressions. If a patient who has progressed dies during DLI therapy or if DLI therapy were to be deemed a unsuccessful for that patient, the date of progression will be the date at which the original progression was first documented. The starting time for PFS will be day 0 of transplant. The primary statistical endpoint will be the probability of two-year PFS (i.e., being progression-free for at least two-years). This probability will be denoted by p. Given the relatively long window of observation (up to two-years), a single-stage binomial design will be employed. Symmetric error rates of at most $\alpha=\beta= 0.1$ will be used.

15.1 Early Disease cohort

For this cohort, a probability of 2-year PFS ≤ 0.5 will be considered clinically uninteresting. The goal of the study is to evaluate 39 eligible patients for this cohort. If at least 24 out of these 39 patients are progression-free for at least two years, it will be concluded that, at a one-sided level of at most $\alpha= 0.1$, there is sufficient statistical evidence to reject H_0: p=0.5 in favor of the general alternative H_1: p>0.5.

This design will have, at a one-sided level of at most $\alpha= 0.1$, a power of at least $1-\beta= 0.9$ to reject H_0: p=0.5 against the local alternative H_1: $p=p_1= 0.7$. The power against other local alternatives is illustrated in the table below.

p1	0.5	0.55	0.6	0.65	0.7
$1-\beta[p_1]$	0.1	0.256	0.491	0.736	0.906

This table illustrates the power, denoted by $(1-\beta[p_1])$, of testing H_0: p=0.5, at the one-sided $\alpha=0.1$ level, against the local alternative H_1: $p=p_1$, where p denotes the probability of two-year PFS for the early disease cohort.

15.2 Advanced Disease Cohort

For this cohort, a probability of 2-year PFS ≤ 0.3 will be considered clinically uninteresting. The goal of the study is to evaluate n=39 eligible patients for this cohort. Let p denote the probability of two-year PFS. If at least 16 out of these 39 patients are progression-free for at least *two years*, it will be concluded that, at a one-sided level of at most $\alpha= 0.1$, there is sufficient statistical evidence to reject H_0: p=0.3 in favor of the general alternative H_1: p> 0.3.

This design will have, at a one-sided level of at most $\alpha= 0.1$, a power of at least $1-\beta= 0.1$ to reject H_0: p=0.3 against the local alternative H_1: $p=p_1= 0.5$. The power against other local alternatives is illustrated in the table below.

p_1	0.3	0.35	0.4	0.45	0.5
$1-\beta[p_1]$	0.094	0.264	0.509	0.744	0.9

This table illustrates the power, denoted by (1-β[p1]), of testing H_0: p=0.3, at the one-sided α= 0.1 level, against the local alternative H_1: p=p_1 where p denotes the probability of two-year PFS for the advanced disease cohort.

15.3 Secondary Objectives

Other clinical endpoints such as response, acute GVHD, chronic GVHD, treatment-related mortality, overall survival and chimerism for CD3 will be analyzed as secondary endpoints. All secondary hypotheses will be tested at an unadjusted level of 0.05. Discrepancy between censored time-to-event endpoints will be assessed using the log-rank test. Survival distributions will be estimated using the Kaplan-Meier method. Binomial proportions will be estimated using the observed proportion and Clopper-Pearson interval estimator. Proportions will be compared using Fisher's test. The analysis will be done within each cohort.

15.4 Safety Monitoring

We will monitor treatment related mortality (TRM) on a regular basis. TRM is defined as death within the first six months after transplant not secondary to relapse. We expect that the probability of experiencing TRM should be around 0.2. A probability of 0.3 or above would be deemed unacceptable and prompt the study team to reassess the safety of the study regimen. TRM will be assessed in five stages (first 14 and then every other 16 patients). At each stage, we will consider conducting a safety assessment if the cumulative number of TRMs is large. The critical values for each stage are shown in Table 1. The probability of initiating a safety assessment (i.e., cross any of the five boundaries) is shown in Table 1 for a true TRM probability of 0.2, 0.25, 0.3, 0.35 or 0.4. We will estimate the cumulative incidence rate for TRM.

k	1	2	3	4	5
n_k	14	16	16	16	16
N_k	14	30	46	62	78
r_k	8	12	15	19	22

Table 1: Monitoring design for conducting a safety assessment. The stage is denoted by *k*. The number of patients accrued during and up to stage *k* are denoted by n_k and N_k respectively. The critical value at stage *k* is denoted by r_k. For example, if among the first 29 patients evaluable for TRM, there are 12 or more events, a safety assessment will be conducted.

p	p_1	p_2	p_3	p_4	p_5	Early Exit Probability	Exit Probability
0.20	0.004	0.006	0.024	0.017	0.032	0.052	0.084
0.25	0.014	0.032	0.115	0.084	0.129	0.246	0.375
0.30	0.039	0.104	0.271	0.161	0.173	0.574	0.747
0.35	0.085	0.226	0.381	0.152	0.100	0.845	0.945
0.40	0.158	0.367	0.359	0.081	0.029	0.965	0.994

Table 3: The operating characteristics for the safety assessment monitoring rule illustrated in Table 2. The probability of experiencing a TRM is denoted by p. The first exit probability at stage *k* is denoted by p_k. An "exit" would initiate a safety assessment. The probability of early exit is equal to p_1+...+p_4. The exit probability is equal to p_1+...+p_5.

15.5 Sample Size, Study Duration and Follow-up

A total of n = 78 (39+39) patients will be evaluated. To this end, we expect that we may have to register up to 86 patients. As such, the minimum and maximum number of patients to be registered is 78 and 86 respectively. We expect to accrue about 25 patients per year. As such, the accrual period is expected to be between 3 and 3.5 years. The last patient in each cohort will be followed for two-years, so the total study period is expected to be 5 and 5.5 years. Once a cohort has been filled (i.e., 39 evaluable patients have been registered), further accrual to that cohort will be suspended. Given that the proportion of early-disease patients is expected to be about the same as the proportion of advanced-disease patients, the cohorts are expected to be filled around the same time. Patients will be followed for survival at least 5 years from time of registration so as to be able to assess long-term survival.

15.6 Correlative Science Statistical Considerations

Descriptive statistics (i.e. means, standard deviations, 95% confidence intervals for continuous variables, and frequencies for discrete data) will be computed for all correlative laboratory parameters. The association between clinical response, progression free survival, overall survival and toxicity will be examined with respect to correlative biomarkers in an exploratory manner to generate hypotheses for future trials likely involving larger numbers of CLL patients.

16.0 ADVERSE EVENT REPORTING (AER)

CALGB and BMT CTN investigators are required by Federal Regulations to report serious adverse events as defined in sections 16.1 and 16.2. Investigators are required to notify the Investigational Drug Branch, CALGB Central Office, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP Web site at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE. All reactions determined to be reportable in an expedited manner must be reported using the NCI Adverse Event Expedited Reporting System (AdEERS). Reporting of cases of secondary AML/MDS should be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using Study Form C-1001.

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

16.1 CALGB 100701 Adverse Event Reporting Requirements

Phase 2 and 3 Trials: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Treatment[2]

	Grade 1	Grade 2	Grade 3		Grade 3		Grade 4	Grade 4	Grade 5[3]	Grade 5[3]
			Unexpected		Expected					
	Unexpected and Expected	Unexpected and Expected	with Hospitalization	without Hospitalization	with Hospitalization	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 or non-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.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP or non-CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

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

- All adverse events reported via AdEERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- A list of specific expected adverse events can be found in Section 11.0 (Drug Formulation, Availability, and Preparation).
- Grade 3/4 myelosuppression is expected during transplantation. Grade 3/4 myelosuppression and hospitalization resulting from such do not require AdEERS, but should be submitted as part of study results.
- AdEERS reports are to be submitted electronically (http://ctep.info.nih.gov/reporting/adeers.html) 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.
- 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 7.1 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.

16.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Rituximab

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 986 patients.* Below is the CAEPR for Rituximab.

Version 2.1, March 19, 2010[1]

Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n= 986]			**EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia***
	Blood and lymphatic system disorders - Other (Hyperviscosity: Waldenstrom's)		***Blood and lymphatic system disorders - Other (Hyperviscosity: Waldenstrom's)***
	Febrile neutropenia		***Febrile neutropenia***
CARDIAC DISORDERS			
	Myocardial infarction		***Myocardial infarction***
	Sinus tachycardia		***Sinus tachycardia***
	Supraventricular tachycardia		***Supraventricular tachycardia***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
	Diarrhea		***Diarrhea***
	Nausea		***Nausea***
	Vomiting		***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Chills			***Chills***
	Edema limbs		
	Fatigue		***Fatigue***
Fever			***Fever***
Infusion related reaction			***Infusion related reaction***
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction***
		Anaphylaxis	
	Serum sickness		***Serum sickness***
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection***[2]
	Infections and infestations - Other (Activation of Hepatitis B, C, CMV, parvovirus B19, JC virus,		***Infections and infestations - Other (Activation of Hepatitis B, C, CMV, parvovirus B19, JC***

	varicella zoster, herpes simplex, West Nile virus)		***virus, varicella zoster, herpes simplex, West Nile virus)***
	Infections and infestations - Other (Infection in HIV Positive Patients)		
INVESTIGATIONS			
Lymphocyte count decreased			***Lymphocyte count decreased***
	Neutrophil count decreased		***Neutrophil count decreased***
	Platelet count decreased		***Platelet count decreased***
	White blood cell decreased		***White blood cell decreased***
METABOLISM AND NUTRITION DISORDERS			
	Hyperglycemia		
	Hypocalcemia		***Hypocalcemia***
	Hypokalemia		
		Tumor lysis syndrome	***Tumor lysis syndrome***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia***
	Back pain		
	Myalgia		***Myalgia***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		***Tumor pain***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness***
	Headache		***Headache***
	Lethargy		
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
	Seizure		***Seizure***
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Adult respiratory distress syndrome	
	Allergic rhinitis		
	Bronchospasm		***Bronchospasm***
	Cough		***Cough***
	Dyspnea		***Dyspnea***
	Hypoxia		***Hypoxia***
	Pneumonitis		***Pneumonitis***
	Sore throat		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	***Erythema multiforme***
	Hyperhidrosis		***Hyperhidrosis***
	Pruritus		***Pruritus***
	Rash maculo-papular		***Rash maculo-papular***
	Skin and subcutaneous tissue disorders - Other (angioedema)		
		Stevens-Johnson syndrome	***Stevens-Johnson syndrome***
		Toxic epidermal necrolysis	***Toxic epidermal necrolysis***
	Urticaria		***Urticaria***
VASCULAR DISORDERS			
	Flushing		***Flushing***

	Hypertension		***Hypertension***
	Hypotension		***Hypotension***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

Also reported on rituximab trials but with the relationship to rituximab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (cyanosis); Left ventricular systolic dysfunction; Sinus bradycardia; Ventricular fibrillation
EYE DISORDERS - Conjunctivitis; Eye disorders - Other (ocular edema); Uveitis; Watering eyes
GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Dysphagia; Gastrointestinal obstruction[3]; Gastrointestinal perforation[4]; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=Grade 2 Lymphopenia)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture
INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Investigations - Other (hyperphosphatemia); Investigations - Other (LDH increased); Weight loss
METABOLISM AND NUTRITION DISORDERS - Anorexia; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoglycemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis
NERVOUS SYSTEM DISORDERS - Nervous system disorders - Other (Cranial Neuropathy NOS); Peripheral motor neuropathy; Peripheral sensory neuropathy; Pyramidal tract syndrome; Reversible posterior leukoencephalopathy syndrome; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Depression; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Pharyngolaryngeal pain; Pleural effusion; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Skin and subcutaneous tissue disorders - Other (paraneoplastic pemphigus)
VASCULAR DISORDERS - Phlebitis; Thromboembolic event; Vasculitis

Note: Rituximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

17.0 REFERENCES

1. Keating, M.J., et al., Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood, 2002. 99(10): p. 3554-61.

2. Byrd, J.C., et al., Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. Blood, 2005. 105(1): p. 49-53.

3. Keating, M.J., et al., Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol, 2005. 23(18): p. 4079-88.

4. Wierda, W., et al., Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol, 2005. 23(18): p. 4070-8.

5. Gribben, J.G., et al., Autologous and allogeneic stem cell transplantations for poor-risk chronic lymphocytic leukemia. Blood, 2005. 106(13): p. 4389-96.

6. Pavletic, Z., et al., High Incidence of Relapse After Autologous Stem-Cell Transplantation for B-Cell Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Annals of Oncology, 1998. 9(9): p. 1023-1026.

7. Dreger, P., et al., Prognostic Factors for Survival after Autologous Stem Cell Transplantation for Chronic Lymphocytic Leukemia: the EBMT Experience. Blood, 2000. 96: p. 482a (abstract).

8. Esteve, J., et al., Stem Cell Transplantation for Chronic Lymphocytic Leukemia: Outcome and Prognostic Factors after Autologous and Allogeneic Transplants. Blood, 2001. 98: p. 482a (abstract).

9. Ritgen, M., et al., Unmutated immunoglobulin variable heavy-chain gene status remains an adverse prognostic factor after autologous stem cell transplantation for chronic lymphocytic leukemia. Blood, 2003. 101(5): p. 2049-53.

10. Damle, R.N., et al., Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood, 1999. 94(6): p. 1840-7.

11. Dohner, H., et al., Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med, 2000. 343(26): p. 1910-6.

12. Hamblin, T.J., et al., Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood, 1999. 94(6): p. 1848-54.

13. Dohner, H., et al., p53 gene deletion predicts for poor survival and non-response to therapy with purine analogs in chronic B-cell leukemias. Blood, 1995. 85(6): p. 1580-9.

14. Dohner, H., et al., 11q deletions identify a new subset of B-cell chronic lymphocytic leukemia characterized by extensive nodal involvement and inferior prognosis. Blood, 1997. 89(7): p. 2516-22.

15. Sorror, M.L., et al., Hematopoietic Cell Transplantation After Nonmyeloablative Conditioning for Advanced Chronic Lymphocytic Leukemia. J Clin Oncol, 2005. 23: p. 3819-29.

16. Brown, J., et al., Predictors of Improved Progression-Free Survival Following Nonmyeloablative Allogeneic Stem Cell Transplantation for Advanced CLL. Biology of Blood and Marrow Transplantation, 2006. in press.

17. Caballero, D., et al., Allogeneic transplant with reduced intensity conditioning regimens may overcome the poor prognosis of B-cell chronic lymphocytic leukemia with unmutated immunoglobulin variable heavy-chain gene and chromosomal abnormalities (11q- and 17p-). Clin Cancer Res, 2005. 11(21): p. 7757-63.

18. Delgado, J., et al., Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. Blood, 2006. 107(4): p. 1724-30.

19. Khouri, I.F., et al., Long-term follow-up of patients with CLL treated with allogeneic hematopoietic transplantation. Cytotherapy, 2002. 4(3): p. 217-21.

20. Pavletic, S.Z., et al., Unrelated donor marrow transplantation for B-cell chronic lymphocytic leukemia after using myeloablative conditioning: results from the Center for International Blood and Marrow Transplant research. J Clin Oncol, 2005. 23(24): p. 5788-94.

21. Khouri, I.F., et al., Concurrent administration of high-dose rituximab before and after autologous stem-cell transplantation for relapsed aggressive B-cell non-Hodgkin's lymphomas. J Clin Oncol, 2005. 23(10): p. 2240-7.

22. Horwitz, S.M., et al., Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. Blood, 2004. 103(3): p. 777-83.

23. Brugger, W., et al., Rituximab consolidation after high-dose chemotherapy and autologous blood stem cell transplantation in follicular and mantle cell lymphoma: a prospective, multicenter phase II study. Ann Oncol, 2004. 15(11): p. 1691-8.

24. Khouri, I.F., et al., Nonablative allogeneic stem cell transplantation for chronic lymphocytic leukemia: impact of rituximab on immunomodulation and survival. Experimental Hematology, 2004. 32(1): p. 28-35.

25. Cutler, C., et al., Rituximab for steroid-refractory chronic graft-vs.-host disease. Blood, 2006.

26. Michallet, M., et al., HLA-identical sibling bone marrow transplantation in younger patients with chronic lymphocytic leukemia. European Group for Blood and Marrow Transplantation and the International Bone Marrow Transplant Registry. Ann Intern Med, 1996. 124(3): p. 311-5.

27. Khouri, I.F., et al., Allogeneic blood or marrow transplantation for chronic lymphocytic leukaemia: timing of transplantation and potential effect of fludarabine on acute graft-versus-host disease. Br J Haematol, 1997. 97(2): p. 466-73.

28. Khouri, I.F., et al., Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. J Clin Oncol, 1998. 16(8): p. 2817-24.

29. Schetelig, J., et al., Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. J Clin Oncol, 2003. 21(14): p. 2747-53.

30. Krackhardt, A.M., et al., T-cell responses against chronic lymphocytic leukemia cells: implications for immunotherapy. Blood, 2002. 100(1): p. 167-73.

31. Harig, S., et al., Induction of cytotoxic T-cell responses against immunoglobulin V region-derived peptides modified at human leukocyte antigen-A2 binding residues. Blood, 2001. 98(10): p. 2999-3005.

32. Krackhardt, A.M., et al., Identification of tumor-associated antigens in chronic lymphocytic leukemia by SEREX. Blood, 2002. 100(6): p. 2123-31.

33. Trojan, A., et al., Immunoglobulin framework-derived peptides function as cytotoxic T-cell epitopes commonly expressed in B-cell malignancies. Nat Med, 2000. 6(6): p. 667-72.

34. Sahin, U., O. Tureci, and M. Pfreundschuh, Serological identification of human tumor antigens. Curr Opin Immunol, 1997. 9(5): p. 709-16.

35. Bellucci, R., et al., Complete response to donor lymphocyte infusion in multiple myeloma is associated with antibody responses to highly expressed antigens. Blood, 2004. 103(2): p. 656-63.

36. Schetelig, J., et al., Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17p deletion: a retrospective European Group for Blood and Marrow Transplantation analysis. J Clin Oncol, 2008. 26(31): p. 5094-100.

37. Sorror, M.L., et al., Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol, 2008. 26(30): p. 4912-20.

38. Gorgun, G., et al., Chronic lymphocytic leukemia cells induce changes in gene expression of CD4 and CD8 T cells. J Clin Invest, 2005. 115(7): p. 1797-805.

39. Byrd, J.C., et al., Select high-risk genetic features predict earlier progression following chemoimmunotherapy with fludarabine and rituximab in chronic lymphocytic leukemia: justification for risk-adapted therapy. J Clin Oncol, 2006. 24(3): p. 437-43.

40. Dierksheide, J.E., et al., IFN-gamma gene polymorphisms associate with development of EBV+ lymphoproliferative disease in hu PBL-SCID mice. Blood, 2005. 105(4): p. 1558-65.

41. Lin, T.S., et al., FCGR3A and FCGR2A polymorphisms may not correlate with response to alemtuzumab in chronic lymphocytic leukemia. Blood, 2005. 105(1): p. 289-91.

42. Hallek, M., et al., Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood, 2008. 111(12): p. 5446-56.

43. Przepiorka, D., et al., Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant, 1994. 15(6): p. 825-8.

44. Cheson, B.D., et al., National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood, 1996. 87(12): p. 4990-7.

18.0 RELATED DONOR MODEL CONSENT FORM

A Phase II Study of Reduced-Intensity Allogeneic Transplant for Patients with High-Risk Chronic Lymphocytic Leukemia

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to participate in this trial because you are being considered as a donor for a sibling, that is a brother or sister, that has been diagnosed with chronic lymphocytic leukemia (CLL). Donors that are identified as an HLA-identical sibling have the same type of bone marrow and can server as a good donor of "stem cells" for a family member diagnosed with leukemia.

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 chronic lymphocytic leukemia (CLL), 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. Your sibling is considered to have CLL with high-risk features that may not respond to standard forms of treatment such as chemotherapy.

Instead, a transplant of some of sibling's "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. After transplant into the patient, the donor's stem cells (cells that have the ability to develop into red blood cells, white blood cells, or platelets) appear to have the ability to recognize and kill the patient's leukemia cells. This powerful reaction performed by the donor's stem cells is known as the "graft-versus-leukemia," or GVL, effect. The use 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?

As many as 86 people will take part in this study.

What will happen if I take part in this research 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 class of drugs known as colony stimulating factors (or CSFs for short). CSFs are commercially available and approved medications used in patients receiving chemotherapy for cancer to increase the number of white blood cells, the cells responsible for fighting infections. When CSFs are 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 stem cells that can then be used for transplant in their siblings who have cancer. When combined with chemotherapy in the patient with cancer, 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.

Your sibling's study doctor will describe the specific treatment to be given to you to collect the stem cells. Generally, the CSF is given to you, the donor, for several consecutive days as a daily injection just underneath the skin (subcutaneous injection). You or a family member will be taught to give the injections at home. During the period in which you are receiving the CSF, your white blood cell count will increase. After you complete the CSF, 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 the CSF. No more than three leukapheresis procedures should be necessary. Each collection of stem cells will then be transfused directly into the patient (your brother or sister) who in the meantime will have received 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.

Some or all of the stem cells that are collected from you during the leukapheresis procedure may be frozen to preserve them prior to infusing them into your sibling. Also, some of the cells that are frozen may not be needed by your sibling. If some or all of the cells are not used by your sibling, your cells will be stored. The remaining stored cells may be discarded if your sibling's study doctor determine that there is no clinical need for these cells.

If your sibling's disease should return during the course of their participation in this trial, there is a chance that your sibling's study doctor may request more cells from you. This would be done to further treat your sibling's disease.

How long will I be in the study?

You will be in the study for about 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.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the CSF. In some cases, side effects can be serious, long lasting, or may never go away.

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.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to CSFs include those which are:

Likely

- Bone pain.
- Fatigue
- Muscle aches.

Less Likely

- Fever.
- Chills.
- Rash.

Rare

- Shortness of breath.
- Nausea.
- Vomiting.
- Diarrhea.
- Headache.
- Chest pain.
- Hair loss.
- Loss of appetite.
- Weakness.
- Low blood pressure.
- Increased liver function tests.
- In extremely rare cases, rupture of the spleen has been reported following CSF treatment. If you develop abdominal pain while taking CSF you should inform your doctor immediately.

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 your study doctor.

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 choices do I have if I do not take part in this study?

Your participation in this study is voluntary.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Cancer and Leukemia Group B (CALGB)
- Blood and Marrow Transplant Clinical Trial Network (BMT CTN)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.

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)_____.

The CALGB has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services or for purpose of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of the CSF in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

Related Research Studies

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any this additional study.

You can say "yes" or "no" to the following study. Please mark your choice for the study.

About Using Blood for Research

During the course of determining whether you are a suitable donor, your sibling's doctor will obtain blood specimens to do some tests. The results of these tests will be given to you by your sibling's doctor and will be used to plan their care. We would like to collect an additional blood specimen (about 2 tablespoonfuls) at this time. This sample would be obtained when other routine laboratories are obtained so you will not need to undergo additional procedures to collect this specimen. We will analyze this sample in the laboratory to see if we can determine how the donor's cells recognize the patient's leukemia cells, and how the patient's immune system recovers after the transplant. The results of these blood studies are for research use only and the results will not be available or used to guide your treatment.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. I agree that my specimens may be used for the research studies described above.

Yes *No*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

19.0 RECIPIENT MODEL CONSENT FORM

A Phase II Study of Reduced-Intensity Allogeneic Transplant for Patients with High-Risk Chronic Lymphocytic Leukemia

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to participate in this trial because you have been diagnosed with chronic lymphocytic leukemia (CLL) that either is considered to have high risk factors or has returned despite previous therapy. Patients considered to have CLL with high-risk features at diagnosis may not respond to standard chemotherapy.

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 outcomes of patients diagnosed with chronic lymphocytic leukemia who may have high risk features or who have had their disease return after receiving chemotherapy.

There is evidence that "stem cells" donated from a sibling (that is, a brother or sister) or another compatible person can be used as part of an effective therapy for CLL. After transplant into the patient, the donor's stem cells (cells that have the ability to develop into red blood cells, white blood cells, or platelets) appear to have the ability to recognize and kill the patient's leukemia cells. This powerful reaction performed by the donor's stem cells is known as the "graft-versus-leukemia," or GVL, effect.

In the past, stem cell transplantation required high doses of chemotherapy and/or radiation in the patient immediately prior to infusion of the donor's stem cells. Success in controlling or eliminating cancer was believed to be the result of a combination of the high-dose chemotherapy/radiotherapy and the GVL effect described above. The high doses of chemotherapy and/or radiation and the serious side effects that result from it, restricted its use in young patients or patients without other significant medical problems. Recently, success has been had using lower doses of chemotherapy without radiation; the lower doses of chemotherapy have reduced and/or eliminated some of the serious side effects. When lower doses of chemotherapy without radiation are used, these types of transplants are referred to as "reduced intensity" transplants. The reduced intensity transplant in this study is considered standard, but the use of transplant early as an option for patients with high-risk features is considered experimental. The use of rituximab after the reduced intensity transplant is also considered experimental.

How Many People Will Take Part in the Study?

As many as 86 people will take part in this study. It is anticipated that approximately 39 people diagnosed with CLL with high risk features, and 39 people diagnosed with CLL whose disease has returned despite treatment with chemotherapy will be enrolled.

What will happen if I take part in this research 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 and are all part of regular cancer care. They are routine. Depending on when you last had them, you may need to repeat some of these tests:

- Blood tests
- Physical Exam
- CT scan of your chest, abdomen, pelvis
- Pulmonary Function Tests (PFT) (a test of lung function)
- Echocardiogram or MUGA (a test of heart function)
- Hepatitis, HIV Test
- Bone marrow aspirate and biopsy
- Pregnancy test (if you are a woman of child-bearing potential)

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.

Treatment

The standard treatment for your disease is chemotherapy. This research study will attempt to use a different approach that will use a donor's stem cells to fight your disease. The donor's stem cells will be obtained either from a well-matched relative or from a well-matched individual unrelated to you. The chemotherapy to be given to you during the stem cell transplant is meant to weaken your immune system (including the white blood cells responsible for fighting infections) in preparation for the introduction of your donor's stem cells. The goals of this study are: 1) to replace the leukemic cells responsible for your disease with normal cells from your donor with transplant, and 2) after transplant, to use another drug, called rituximab, to help eliminate any residual or remaining CLL cells. During the transplant component of this research study, your study doctor will recommend one of two transplant chemotherapy treatments, as well as one of two treatments to prevent a specific side effect from transplantation, known as graft-versus-host disease. Graft versus host disease (GVHD) is a side effect of bone marrow or stem cell transplantation. Your donor's stem 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.

Transplant Chemotherapy Treatment #1

Transplant chemotherapy treatment #1 uses the drugs fludarabine, busulfan, and rituximab. The drugs will be given to you by intravenous (IV) infusion, that is through a needle in a vein in your

arm or through a "central line," a catheter (or tube) placed in the large vein under your collarbone or your neck. The day your donor's stem cells will be given to you will be known as Day 0 or the day of transplant. In the description of the treatment that follows, when a drug is given before Day 0, the day of transplant, it will be noted with a negative sign (-). For example, -7 means seven days before Day 0, the day of transplant. When a drug is given after Day 0, the day of transplant, it will be noted with a positive sign (+). For example, +7 means seven days after Day 0, the day of transplant. The first drug to be given will be rituximab. Rituximab will be given by IV infusion on four separate days one week apart. Rituximab will be given on Days -7, -1, +7, and +14 (that is, rituximab will be given seven days *before* Day 0, one day *before* Day 0, seven days *after* Day 0, and fourteen days *after* Day 0). Fludarabine will be given by IV infusion over 30 minutes each day for four (4) days. Fludarabine will be given on Day -5 through Day -2 (that is, fludarabine will be given five days *before* Day 0, the day you receive your donor's stem cells). Busulfan, another chemotherapy drug, will be given also by IV infusion for four days. Busulfan will be given on Days -5 through -2 (that is, busulfan will be given five days *before* Day 0, the day you receive your donor's stem cells). 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.

In an effort to control "graft versus host disease" (or GVHD for short), one of the side effects of transplant discussed further below, your study doctor will recommend **<u>one</u>** of two the following GVHD treatments:

GVHD Option #1 (available only with Transplant Chemotherapy Treatment #1)
You also would receive the drug known as tacrolimus beginning on Day -2 through approximately Day +180 (that is, approximately 6 months after Day 0). Tacrolimus may be given by IV infusion or orally (by mouth). Patients also will receive sirolimus orally starting on Day –2 and continue until Day +180. Finally, another chemotherapy drug, methotrexate, will be given by IV on Day +1, +3, and +6.

GVHD Option #2
You also would receive the drug known as tacrolimus beginning on Day -2 through approximately Day +180 (that is, approximately 6 months after Day 0). Tacrolimus may be given by IV infusion or orally (by mouth). Finally, another chemotherapy drug, methotrexate, will be given by IV on Day +1, +3, +6 and +11.

Depending on your response to treatment, you may require up to three additional infusions of stem cells from your donor. If necessary, your doctor will discuss these treatments with you and they would occur at eight week intervals separating treatments.

Transplant Chemotherapy Treatment #2
Another treatment your doctor might recommend includes the chemotherapy drugs fludarabine, cyclophosphamide, antithymocyte globulin (or ATG for short), and rituximab. The drugs will be

given to you by intravenous (IV) infusion, that is through a needle in a vein in your arm or through a "central line," a catheter (or tube) placed in the large vein under your collarbone or your neck. The day the donor's stem cells will be given to you will be known as Day 0 or the day of transplant. In the description of the treatment that follows, when a drug is given before Day 0, the day of transplant, it will be noted with a negative sign (-). For example, -7 means seven days before Day 0, the day of transplant. When a drug is given after Day 0, the day of transplant, it will be noted with a positive sign (+). For example, +7 means seven days after Day 0, the day of transplant. The first drug to be given will be rituximab. Rituximab will be given by IV infusion on four separate days one week apart. Rituximab will be given on Days -7, -1, +7, and +14 (that is, rituximab will be given seven days *before* Day 0, one day *before* Day 0, seven days *after* Day 0, and fourteen days *after* Day 0) If your donor is not related to you, antithymocyte globulin (or ATG, for short) will be given you to you over six hours on Days -6, -5, and -4 (that is, for three days beginning six days *before* Day 0). Fludarabine will be given by IV infusion over 30 minutes each day for four (4) days on Day -5 through Day -2 (that is, fludarabine will be given five days *before* Day 0). Cyclophosphamide will be given by IV infusion also on Days -5, -4, and -3 (that is, for three days beginning five days *before* Day 0). 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.

GVHD Option #2: In an effort to control "graft versus host disease" (or GVHD for short), one of the side effects of transplant discussed further below, you also would receive the drug known as tacrolimus beginning on Day -2 through approximately Day +180 (that is, approximately 6 months after Day 0). Tacrolimus may be given by IV infusion or orally (by mouth). Finally, another chemotherapy drug, methotrexate, will be given by IV on Day +1, +3, +6 and +11.

Depending on your response to treatment, you may require up to three additional infusions of stem cells from your donor. If necessary, your doctor will discuss these treatments with you and they would occur at eight week intervals separating treatments.

Post Transplant Rituximab Maintenance Treatment
All patients, regardless of which transplant chemotherapy treatment is selected by their study doctor, will receive rituximab maintenance therapy every three months for one year beginning three months after Day 0 of transplant. A total of four rituximab maintenance treatments will be given (Month 3, 6, 9, and 12). Blood tests will be obtained every three months during rituximab maintenance therapy.

At any point during your treatment, your doctor may recommend that you take a hormone called G-CSF (granulocyte colony-stimulating factor).

How long will I be in the study?

While undergoing transplant on this study, you will be seen frequently by your study doctor and have laboratory tests. Blood tests will be obtained every three months during the second year, and then every six months for a maximum of 5 years from study entry. CT scans of the chest,

abdomen, and pelvis will be obtained 3 months, 12 months, and 24 months after Day 0 of transplant. While receiving rituximab maintenance therapy, you will be monitored by your study doctor each month prior to rituximab treatments at 3, 6, 9 and 12 months after Day 0. After you complete all treatment on this study, you will then need to be seen by your study doctor and have laboratory tests every six months for a maximum of five years from the date of entry on the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your study doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

The risks and side effects you may experience in this study will be based on the chemotherapy and GVHD treatments your study doctor chooses for you. Below you will find the risks and side effects identified by the treatment (both the transplant **and** the rituximab maintenance treatment) and GVHD treatment.

Risks and side effects related to Transplant Chemotherapy Treatment #1 (Fludarabine, Busulfan, and Rituximab) include:

Likely

- Lowered white blood cell count[v] (neutrophils/granulocytes) that may lead to infection.

- Lowered platelets[v] which may lead to an increase in bruising or bleeding.
- Lowered red blood cells[v] which may cause anemia, tiredness, or shortness of breath.
- Nausea.
- Vomiting.
- Decreased number of a different type of white blood cells (lymphocytes) that may lead to infection.
- Irritation or sores in the lining of the digestive tract (for example, mouth, throat, esophagus, anus, etc.).
- Infusion reactions with rituximab including fever, chills, and nausea which can be severe.
- Loss of appetite and/or weight loss.
- Fatigue.
- Time away from work.
- Hair loss.

[v] Should this occur, it can be treated with blood products (transfusions) and antibiotics.

Less Likely

- Hypertension (high blood pressure) which may require treatment.
- Swelling of the arms or legs.
- High blood sugar level.
- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Your doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection.
- Some other viral infections may be worsened or reactivated from a "sleeping" state in patients with impaired immune function or who receive rituximab.
- Headache.
- Inflammation of the lungs which can cause difficulty breathing and difficulty getting oxygen.
- Infection which occurs due to a decreased number of a type of white blood cells.
- Rejection of your donor's stem cells.
- Graft versus host disease (see below).
- Darkening of the skin.
- Sore throat.
- Abdominal pain.
- Rash or itching.

- Swelling of the lips, eyes, tongue, and throat which can be severe.
- Allergic reaction.
- Stuffy or runny nose, sneezing.
- Allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands.
- Abnormal fast heart beat.
- Decreased blood supply to the heart/heart attack.
- Low blood pressure.
- Excessive sweating.
- Flushing.
- Hives.
- Diarrhea.
- Low blood potassium.
- Dizziness.
- Seizure.
- Pain in the back, joints, or muscles.
- Irritation of the small airways or wheezing.
- Cough.
- Shortness of breath.

Rare But Serious

- Severe reactions during rituximab infusions or severe allergic reaction: a fast heart rate, wheezing, low blood pressure, sweating, swelling of the throat, and face rash may occur within a few minutes of starting treatment. They can be handled with medications and sometimes by slowing the rate of infusion. The reactions are more common during the first infusion of rituximab. You will be given medications to decrease the likelihood that the reactions may occur, and decrease their severity if they should occur.
- Destruction of red blood cells that may be life-threatening.
- Another one of these viral infections causes a serious brain condition called progressive multifocal leukoencephalopathy (PML). PML can be serious causing severe disability or death.
- Vision changes and confusion.
- Abnormal clotting of blood in small blood vessels.
- Rash which may become severe.

- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer.
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of the skin to separate from the middle layer.
- Liver damage that can be severe.
- Infertility/inability to produce children.
- Severe lung dysfunction resulting in the inability to breathe which can be life-threatening.
- Inflammation of the bladder that may cause blood to be present in the urine.
- Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment.

Risks and side effects related to Transplant Chemotherapy Treatment #2 (<u>Fludarabine, Cyclophosphamide, ATG and Rituximab</u>) include:

<u>Likely</u>

- Lowered white blood cell count[v] (neutrophils/granulocytes) that may lead to infection.
- Lowered platelets[v] which may lead to an increase in bruising or bleeding.
- Lowered red blood cells[v] which may cause anemia, tiredness, or shortness of breath.
- Nausea.
- Vomiting.
- Fatigue.
- Irregular menstrual periods in women.
- Hair loss.
- Pain in the abdomen.
- Decreased number of a different type of white blood cells (lymphocytes) that can lead to infection.
- Infusion reactions with rituximab including fever, chills, and nausea which can be severe.
- Irritation or sores in the lining of the digestive tract (for example, mouth, throat, esophagus, anus, etc.).
- Loss of appetite and/or weight loss.
- Time away from work.

[v] Should this occur, it can be treated with blood products (transfusions) and antibiotics.

Less Likely

- High blood sugar level.
- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Your doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection.
- Some viral infections may be worsened or reactivated from a "sleeping" state in patients with impaired immune function or who receive rituximab.
- Low blood potassium level.
- Headache.
- Swelling of the arms or legs
- Rash, itching.
- Pain in the back, joint, or muscles.
- Lung damage.
- Graft versus host disease (see below).
- Rejection of your donor's stem cells.
- Infection which occurs due to a decreased number of a type of white blood cells.
- Shortness of breath.
- Allergic reaction.
- Stuffy or runny nose, sneezing.
- Allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands.
- Abnormal fast heart beat.
- Abdominal pain.
- Sore throat.
- Decreased blood supply to the heart/heart attack.
- Low blood pressure.
- High blood pressure.
- Excessive sweating.
- Flushing.
- Hives.
- Diarrhea.
- Dizziness.

- Seizure.
- Pain in the back, joints, or muscles.
- Irritation of the small airways or wheezing.
- Cough.
- Inflammation of the lungs which can cause difficulty breathing and difficulty getting oxygen.
- Swelling of the lips, eyes, tongue and throat which can be severe.

Rare But Serious

- Severe reactions during rituximab infusions or severe allergic reaction: a fast heart rate, wheezing, low blood pressure, sweating, swelling of the throat, and face rash may occur within a few minutes of starting treatment. They can be handled with medications and sometimes by slowing the rate of infusion. The reactions are more common during the first infusion of rituximab. You will be given medications to decrease the likelihood that the reactions may occur, and decrease their severity if they should occur.
- Destruction of red blood cells that may be life-threatening.
- Another one of these viral infections causes a serious brain condition called progressive multifocal leukoencephalopathy (PML). PML can be serious causing severe disability or death.
- Abnormal clotting of blood in small blood vessels.
- Liver damage that can be severe.
- Rash which may become severe.
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer.
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of the skin to separate from the middle layer.
- Vision changes and confusion.
- Inflammation of the bladder that may cause blood to be present in the urine.
- Infertility/inability to produce children.
- Severe skin and gut lining reaction that may include rash and sloughing or death of tissue.
- Severe lung dysfunction resulting in the inability to breathe which can be life-threatening.
- Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment.

Risks and side effects related to GVHD Option #1 (Tacrolimus, Sirolimus, Methotrexate) include:

Likely

- Lowered red blood cells[ψ] which may cause anemia, tiredness, or shortness of breath.
- Lowered white blood cell count[ψ] that may lead to infection.
- Lowered platelets[ψ] which may lead to an increase in bruising or bleeding.
- Hypertension (high blood pressure).
- Headache.
- Tremors.
- Difficulty sleeping or falling asleep.
- Condition of the nervous system that causes numbness, tingling, or burning sensation.
- Increased blood potassium level.
- Decreased blood potassium level.
- Decreased blood phosphate level.
- Decreased blood magnesium level.
- Nausea.
- Vomiting.
- Loss of appetite.
- Constipation.
- Diarrhea.
- Abdominal pain.
- Fever.
- Fatigue.
- Increased blood level of an enzyme from muscle.
- Increased blood cholesterol level.
- Weight gain.
- Joint pain.
- Shortness of breath.
- Increased sensitivity to sunlight.

[ψ] Should this occur, it can be treated with blood products (transfusions) and antibiotics.

Less Likely

- Acne/pimples.

- Rash/itching.
- Hives.
- Infection of the mouth when the white blood cell count is low.
- Infection of the urinary tract when the white blood cell count is low.
- Inflammation or infection of the bladder.
- Chest pain.
- Back pain.
- Upset stomach or heartburn.
- Irritation or sores in the lining of the digestive tract (for example, mouth, throat, esophagus, anus, etc.).
- Dizziness.
- Agitation.
- Anxiety.
- Confusion.
- Convulsion or seizures.
- Depression.
- Hallucinations/delusions.
- Weakness or loss of function caused by damage to nerves.
- Involuntary muscle movement.
- Increased blood level of uric acid, a waste material from food digestion.
- Kidney damage.
- Liver damage.
- Inflammation or infection of the bladder that might result in blood in the urine.
- Fluid collection in the abdomen.
- Swelling of the arms, legs, head or neck, or trunk of the body.
- Increased blood sugar level.
- Blurred vision.
- Ringing in the ears.

Rare But Serious

- Destruction of red blood cells that may be life-threatening.
- Bleeding.

- Severe life-threatening damage to the lungs which can lead to fluid in the lungs.

Risks and side effects related to GVHD Option #2 (Tacrolimus, Methotrexate) include:

Likely

- Lowered red blood cells[ψ] which may cause anemia, tiredness, or shortness of breath.
- Lowered white blood cell count[ψ] that may lead to infection.
- Lowered platelets[ψ] which may lead to an increase in bruising or bleeding.
- Hypertension (high blood pressure).
- Headache.
- Tremors.
- Difficulty sleeping or falling asleep.
- Condition of the nervous system that causes numbness, tingling, or burning sensation.
- Increased blood potassium level.
- Decreased blood potassium level.
- Decreased blood phosphate level.
- Decreased blood magnesium level.
- Nausea.
- Vomiting.
- Loss of appetite.
- Constipation.
- Diarrhea.
- Fever.
- Fatigue.
- Increased sensitivity to sunlight.

[ψ] Should this occur, it can be treated with blood products (transfusions) and antibiotics.

Less Likely

- Rash/itching.
- Hives.
- Infection of the mouth when the white blood cell count is low.
- Inflammation or infection of the bladder.

- Chest pain.
- Back pain.
- Irritation or sores in the lining of the digestive tract (for example, mouth, throat, esophagus, anus, etc.).
- Dizziness.
- Agitation.
- Anxiety.
- Confusion.
- Convulsion or seizures.
- Depression.
- Hallucinations/delusions.
- Involuntary muscle movement.
- Increased blood level of uric acid, a waste material from food digestion.
- Kidney damage.
- Liver damage.
- Inflammation or infection of the bladder that might result in blood in the urine.
- Swelling of the arms, legs, head or neck, or trunk of the body.
- Increased blood sugar level.
- Blurred vision.
- Ringing in the ears.

Rare But Serious

- Destruction of red blood cells that may be life-threatening.
- Bleeding.
- Severe life-threatening damage to the lungs which can lead to fluid in the lungs.

Risks and Side Effects Related to Post Transplant Rituximab Maintenance Treatment (all patients will receive rituximab maintenance therapy)

Likely

- Decreased number of a different type of white blood cells (lymphocytes) that can lead to infection.
- Infusion reactions with rituximab including fever, chills, and nausea which can be severe.

Less Likely

- Fatigue.

- Allergic reaction.
- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Your doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection.
- Some viral infections may be worsened or reactivated from a "sleeping" state in patients with impaired immune function or who receive rituximab.
- Stuffy or runny nose, sneezing.
- Allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands.
- Lowered white blood cell count[v] (neutrophils/granulocytes) that may lead to infection.
- Lowered platelets[v] which may lead to an increase in bruising or bleeding.
- Lowered red blood cells[v] which may cause anemia, tiredness, or shortness of breath.
- Abnormal fast heart beat.
- Decreased blood supply to the heart/heart attack.
- Low blood pressure.
- High blood pressure.
- Excessive sweating.
- Flushing.
- Hives.
- Rash, itching.
- Diarrhea.
- Vomiting.
- Swelling of the arms or legs.
- High blood sugar level.
- Low blood potassium.
- Dizziness.
- Seizure.
- Pain in the back, joints, muscles.
- Sore throat.
- Abdominal pain.
- Shortness of breath.
- Headache.

- Irritation of the small airways or wheezing.
- Cough.
- Inflammation of the lungs which causes difficulty breathing and difficulty getting oxygen.
- Swelling of the lips, eyes, tongue, and throat which can be severe.
- Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of rituximab given to you.

Rare But Serious

- Severe reactions during rituximab infusion or severe allergic reaction: a fast heart rate, wheezing, low blood pressure, sweating, swelling of the throat, and face rash may occur within a few minutes of starting treatment. They can be handled with medications and sometimes by slowing the rate of infusion. The reactions are more common during the first infusion of rituximab. You will be given medications to decrease the likelihood that the reactions may occur, and decrease their severity if they should occur.
- Rash which may become severe.
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer.
- Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of the skin to separate from the middle layer.
- Another one of these viral infections causes a serious brain condition called progressive multifocal leukoencephalopathy (PML). PML can be serious causing severe disability or death.
- Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment.
- Severe lung dysfunction resulting in the inability to breathe which can be life-threatening.

Risk of Graft Versus Host Disease (GVHD)

Symptoms of GVHD may 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)

Symptoms of GVHD can range from mild to severe, and when severe GVHD can be fatal (may cause death). Medications will be given to prevent or reduce the chances of having severe GVHD, and to treat GVHD if it occurs.

The risk of developing moderate to severe GVHD following transplantation of stem cells from a matched related donor is between 30-50%.

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.

Risks and Side Effects Related to Bone Marrow Aspirations and Biopsies

There may be some temporary pain or discomfort associated with these routine procedures, but they are necessary to determine whether you are responding to your therapy. Bone marrow biopsies will be required prior to beginning the study, and 3, 12 and 24 months after Day 0 of transplant.

Secondary Malignancies

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 your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the treatment will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about reduced intensity allogeneic stem cell transplant and rituximab maintenance therapy as treatments for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study, including a bone marrow transplant
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Cancer and Leukemia Group B (CALGB)
- Blood and Marrow Transplant Clinical Trial Network (BMT CTN)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Genentech, the manufacturer of rituximab.

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)_____.

The CALGB has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and

Human Services or for purpose of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Rituximab will be supplied at no charge while you take part in this study. The manufacturer does not cover the cost of getting the rituximab ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the rituximab for some reason. If this would occur, other possible options are:

- You might be able to get the rituximab from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.

- If there is no rituximab available at all, no one will be able to get more and the study would close.

If a problem with getting rituximab occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number)*.

Related Research Studies

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

Things to Think About

Many different types of research use normal or diseased (cancerous) specimens. The two main types of research look at

1. Inherited traits that are passed down in families from one generation to the next. For example, researchers may study DNA from blood cells to learn why some cancers are inherited in families, or why a treatment causes side effects in some people but not in others.

2. Changes that happen after you are born (non-inherited). For example, too much soon exposure can cause changes in cells that lead to skin cancer.

Researchers can study DNA (genes), RNA or proteins. When researchers study genes, it is often called "genetic" research, but there is no clear definition for it at this time. Because of this, we use the terms "inherited" and "non-inherited" to explain your choices for donating specimens.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimen is used for this kind of research, the results will not be put in your health records.

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimen that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Cancer and Leukemia Group B may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

We have many ways to protect the information related to your specimens:

1. Your specimens and information receive a unique code. Researchers only receive coded specimens and information, and will not be able to see the key that links the code to you. Only approved people in the Cancer and Leukemia Group B can match you to the code on your specimens and related information.
2. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information.
3. Research studies are reviewed for the quality of the science and for patient protection before specimens are given to researchers. To make sure the research follows the rules of

the Cooperative Group and state or federal laws, records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies.

4. If research results are published, you will not be identified by name or any other personally identifiable information.

About Using Tissue for Research

Specimens for Research (Non-Inherited Research)

During the course of diagnosing your leukemia, your doctor will obtain blood and bone marrow aspirates to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. Additionally, blood (about 2 tablespoonful) will also be obtained at diagnosis and at about seven time points after the transplant (one month, two months, three months, six months, twelve months, twenty-four months after transplant, and if your CLL should ever return). At diagnosis, it may be possible to obtain about 1 tablespoonful of bone marrow aspirate as well. In addition, if you should undergo donor lymphocyte infusions (DLIs, as described above) we would also like to request 2 tablespoonful of blood afterwards. These samples will be obtained when other routine laboratories are obtained so you will not need to undergo additional procedures to collect these samples. We will analyze these samples in the laboratory to see if we can determine how the donor's cells recognize your leukemia cells, and how your immune system recovers after the transplant. Researchers also will examine the particular characteristics of CLL cells and certain molecular and chromosomal features within these cells. The results of these blood studies are for research use only and the results will not be available or used to guide your treatment.

Specimens for Research (Inherited Research)

Researchers would like to investigate whether substances in your blood are related to the way your body responds (or doesn't respond) to the therapy you receive in this trial. Blood taken before treatment (about 1 tablespoonful) will be used to learn how certain genes influence the effectiveness of this therapy in patients diagnosed with CLL. Blood will be taken only once.

This type of research may find medical conditions that affect you and your blood relatives because it looks at inherited traits. While your genes are unique to you, you share some of them with your blood relatives. It is possible that genetic research may find potential health concerns for you or your family. While this situation is rare, information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

We believe that the risks to you and your family from research on inherited traits are very low. Some states have laws that help to protect against genetic discrimination. A federal law (Genetic Information Non-Discrimination Act, GINA) will help reduce the risk from health insurance or employment discrimination once the law goes into effect. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about the GINA law, you can find information about it on the internet or as your study doctor.

While we believe that the risks to you and your family are very low, we cannot tell you exactly what all of the risk are from taking part in DNA research studies. Your privacy and confidentiality will be protected to the fullest extent possible.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. I agree that my specimens may be used for the research studies (specimens for non-inherited research) described above.

Yes *No*

2. I agree that my specimens may be used for the genetic research studies (specimens for inherited research) described above.

Yes *No*

We would like to keep some of the blood and bone marrow specimens that are left over for inherited and non-inherited research for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases.

3. My specimens may be kept for use in research to learn about, prevent, or treat cancer.

Yes *No*

4. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes *No*

5. Someone may contact me in the future to ask me to take part in more research.

Yes *No*

Where can I get more information?

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

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/

- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX I

IWCLL 2008 Response Criteria

I. COMPLETE RESPONSE

Requires all of the following for a period of at least three months from completion of therapy:

- Absence of lymphadenopathy > 1.5 cm on physical exam and CT scan;
- No hepatomegaly or splenomegaly on physical exam (CT scan may be used to assess);
- No clonal B-cells in the blood by flow cytometry;
- Normal CBC as exhibited by polymorphonuclear leukocytes ≥ 1500/μL, platelets > 100,000/μL, hemoglobin > 11.0 g/dL (untransfused); lymphocyte count < 5,000/μL;
- Bone marrow aspirate and biopsy must be normocellular for age with < 30% of nucleated cells being lymphocytes. Flow cytometry/immunohistochemistry should be performed on bone marrow. Lymphoid nodules may be present but must be T-cell in origin. If these are demonstrated to be clonal B-cells, patients should be considered a partial response. Additionally, if bone marrow is positive by two color flow cytometry for CLL cells it should be considered a partial response. If the marrow is hypocellular a bone marrow should be performed in 2-3 months. If blood counts (polymorphonuclear leukocytes < 1500/μL, platelets < 100,000/μL) fail to recover at the time of the response evaluation but there is otherwise no evidence of CLL otherwise, a repeat determination should be performed at the time of count recovery (polymorphonuclear leukocytes ≥ 1500/μL, platelets > 100,000/μL) but no later than six months.
- Patients who fulfill the criteria for CR after induction with the exception of a persistent cytopenia (CR with incomplete recovery, CRi) that is believed to be treatment related will be considered a CRi. As stated above, patients falling into this category should ideally undergo a repeat bone marrow when counts recover fully. If the bone marrow at this time reveals no CLL, these patients will be considered to be in complete remission at that time. Additionally, patients who fulfill the criteria of CR with exception of having bone marrow lymphoid CLL nodules will be considered a CRi and assessed prospectively for the similarity to outcome with CR.

II. PARTIAL RESPONSE

Requires a ≥ 50% decrease in peripheral lymphocyte count from pre-treatment value, ≥ 50% reduction in lymphadenopathy of as many as 6 measurable lymph nodes, and/or ≥ 50% reduction in splenomegaly/hepatomegaly for a period of at least two months. Patients may have bone marrow lymphoid nodules of B-cell origin. Additionally, these patients must have one of the following:

- Polymorphonuclear leukocytes ≥ 1,500/μL or 50% improvement from pre-treatment value;
- Platelets > 100,000/μL or 50% improvement from pre-treatment value;
- Hemoglobin > 11.0 g/dL (untransfused) or 50% improvement from pre-treatment value

III. PROGRESSIVE DISEASE

Characterized by any one of the following events:

- ≥ 50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥ 2 cm); appearance of new palpable lymph nodes.
- ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5,000/μL.
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes).
- Patients not fulfilling the above criteria for progressive disease but demonstrating a decrease in hemoglobin > 2 g/dL (or < 10 g/dL), decrease > 50% in platelet or granulocyte count will not be rated as progressive disease because these may occur as both a consequence of therapy and of underlying CLL. A bone marrow biopsy in such settings is strongly encouraged.

IV. STABLE DISEASE

Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

APPENDIX II

Ideal Body Weight Table

	Height (Feet/Inch)	Small Frame (kg)	Medium Frame (kg)	Large Frame (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