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

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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*

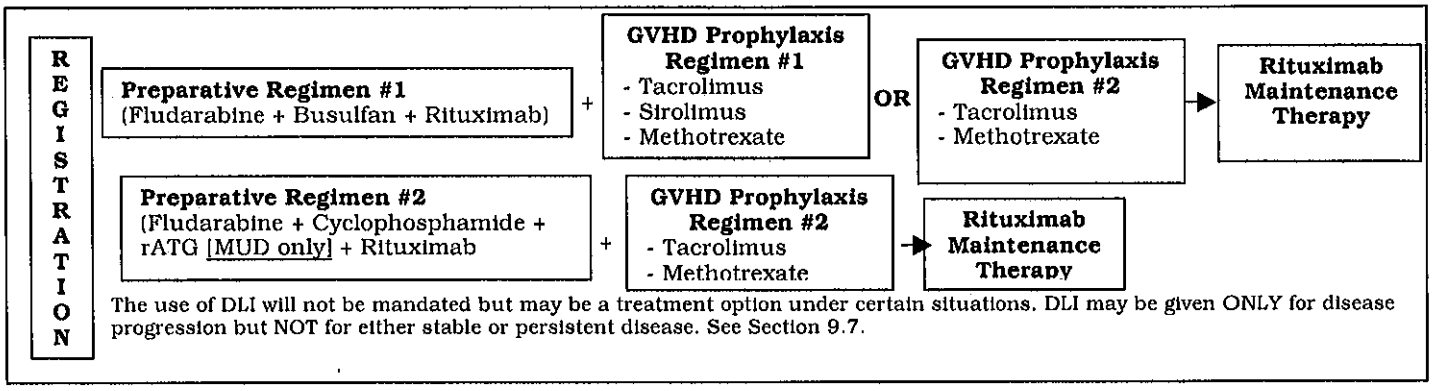
**except for Gilbert's syndrome*

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.

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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.

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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.