SYNOPSIS CLL3C PROTOCOL

Primary objectives
Safety and feasibility of CAMPATH-1H added to (cohort 1) and, in addition, given for four weeks before (cohort 2) myeloablative therapy with PBSCT according to the CLL3 protocol.

Secondary objectives
Clinical as well as molecular remission rate and duration. Overall survival.

Design
Open, non-randomized, multi-center phase II cohort-study.

Duration and patient number
Inclusion of 30 (15 per cohort) patients in 12 months. Interim analysis after 12 months.

Inclusion criteria
Patients with CLL stage Binet B or C, or Binet A at high risk for disease progression (non-nodular marrow infiltration or lymphocyte doubling time < 12 months and thymidine kinase >7.0 U/L or ß-2-microglobuline >3.5mg/L) with all of the following:

- PCR-amplifiable clonal CDRIII rearrangement of the IgV_H
- age 18 - 60 years
- ECOG-performance status 0-1
- no concurrent disease resulting in major organ dysfunction
- written informed consent
- no previous therapy with Dexa-BEAM
- no prior chemotherapy with more than one regimen or longer than 6 months

Treatment schedule (cohort 1: patients 1 to 15)
1. Registration at GCLLSG Study Office, staging, samples for central assessment.
2. Cytoreductive treatment, preferentially according to the FC regimen (2 to 4 cycles).
3. If CR or PR and blood lymphocytes < 10/nL: mobilization with Dexa-BEAM + G-CSF.
4. Collection of: i) unmanipulated PBSC graft (>$2x10^6$/kg CD34+ cells), ii) unmanipulated back-up (>$2x10^6$/kg CD34+ cells and >$1x10^7$/kg CD3+ cells), iii) separate T-cell back-up (optional).
5. If CR or VGPR: Myeloablative therapy with TBI (e.g. 12 Gy) and cyclophosphamide (2 x 60 mg/kg; days -4 to -3) in combination with CAMPATH-1H (days -10 to -8: dose escalation 3, 10, 30 mg; days -6, and -4: 30 mg) and PBSCT (day 0).
6. Prophylaxis with trimethoprim/sulfamethoxazole DS (e.g. Cotrim forte®) three times a week and valaciclovir (e.g. Valtrex®) 3x500mg per day or equivalents for at least six months after PBSCT. Weekly CMV pp65 monitoring and preemptive therapy.
7. Clinical, laboratory and imaging studies (as indicated) and molecular follow-up (CDRIII PCR, blood and marrow) at 1, 3, 6, 12 months after PBSCT and six-monthly thereafter.

Treatment schedule (cohort 2: patients 16 to 30) as above except
5. If CR or VGPR: CAMPATH-1H dose escalation 3 to 30 mg daily, then 30 mg three times weekly for four weeks. Thereafter myeloablative therapy as cohort 1 (see 5. above).

Evaluation criteria and endpoints
Safety: Treatment-related morbidity and mortality.
Feasibility: Patients enrolled and treated according to protocol.
Efficacy: Clinical and molecular remission rates and duration.